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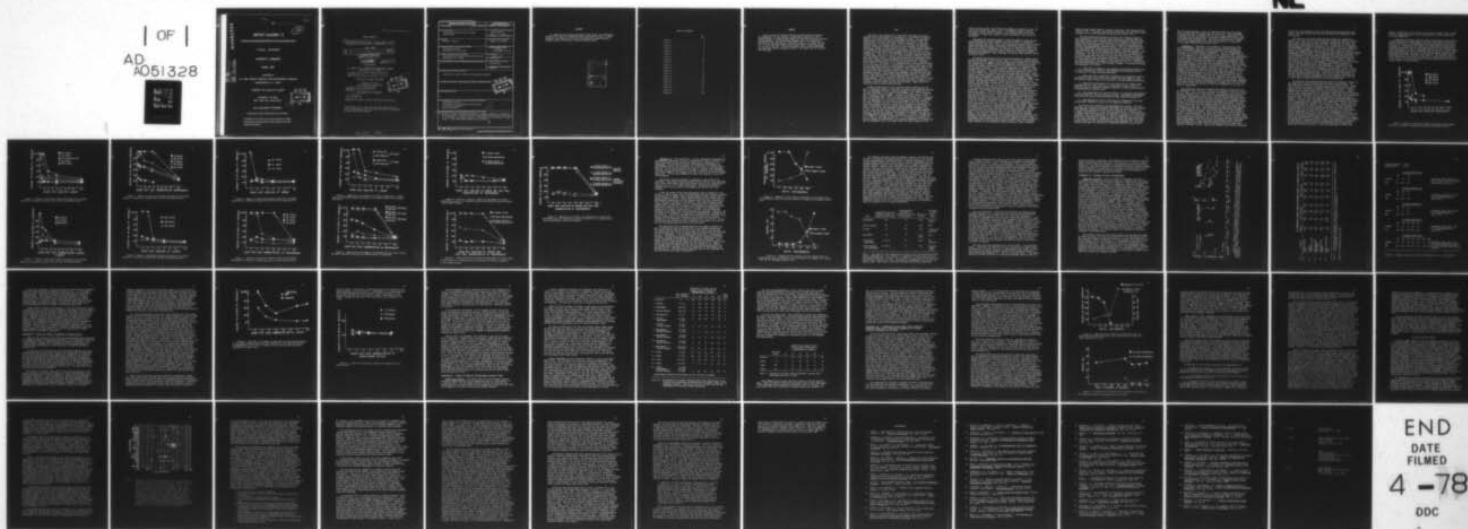
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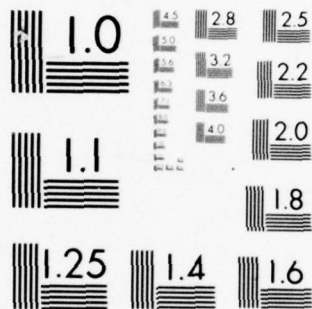
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## REPORT NUMBER 12

A Neuropsychological Basis for Drug Substitution

FINAL REPORT

HAROLD C. NIELSON

APRIL 1977

SUPPORTED BY

U. S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND  
WASHINGTON, D. C. 20314

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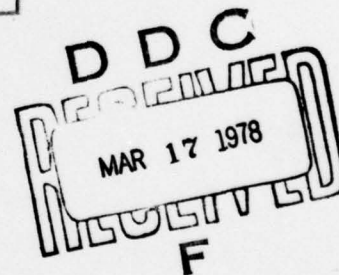
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# FOREWORD

In conducting the research described in this report, the investigator adhered to the "Guide of Laboratory Animal Facilities and Care," as promulgated by the Committee on the Guide for Laboratory Animal Resources, National Academy of Sciences, National Research Council.

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## SUMMARY

In this report the findings from the research previously reported are summarized. We also describe a differential sensitivity of the caudate nucleus to l-dopa between normal cats and those previously addicted to pentobarbital. The conditioned responses (CRs) of the previously addicted cats are abolished by l-dopa while those of the normal cats are not. We also describe attempts to block barbiturate withdrawal seizures in cats and in 240 rats. No reliable method, drug, or drug combination was found that blocked withdrawal seizures. The reasons for this failure were discussed.



## BODY

The goal of this research was to determine what drugs or drug combinations can be substituted for pentobarbital, in pentobarbital addicted animals, to alleviate and/or block withdrawal seizures. This was undertaken because, since the report of Himmelsbach and Andrews (1943) the substitution of one drug for another, either a sedative or a drug cross tolerant with it, has played a major role in the therapy for addiction. Vaillant (1969) has stressed this fact for the initiation of abstinence from heroin (alcohol is substituted for heroin). Further familiar examples on the theme of drug substitution as drug therapy for addiction is the treatment of heroin addicts with methadone, and alcoholics with the minor tranquilizers. The use of drug substitutes as therapy suggested that some of these drugs could also be used to block withdrawal seizures in barbiturate and alcohol addicts. Although these seizures are occasionally fatal, their exact causes are unknown although they are usually attributed to a generalized hypersensitivity of the central nervous system. Goldstein et al. (1974, p. 612) states "It is postulated that a long period of depression of the brain by narcotics, barbiturates, or alcohol could cause a kind of functional denervation of central pathways which sensitizes them so that they over-react when the drug is withdrawn." This presumed hyperexcitability of the central nervous system is thought to be responsible for the withdrawal seizures. The treatment for withdrawal seizures has been some form of drug which depresses the presumed hyperexcitability of the nervous system, thus rendering it no longer "hyperexcitable" and thus aiding in drug withdrawal. As in therapy for addiction, the substitute drug is either a member of the same class of drug as the addicting drug, a sedative, or a drug that is cross tolerant with the addicting drug. Almost always the substitute drug is also an addicting drug.

Another characteristic of the drugs that produce addiction and are used in substitute therapy is that they all produce state dependent learning. This is a phenomena in which a response acquired in the drugged state is lost when the animal is no longer in that drugged state, but it re-appears when the animal is again drugged. Similarly, an animal trained in the sober, non-drugged state, loses the response when drugged, but it re-appears when the drug wears off. Thus the maintenance of the response is dependent upon the maintenance of the drugged or non-drugged state that existed at the time of original learning. We believed that the fact that the same drugs that produce addiction, are used in the treatment of withdrawal, are used in drug therapy, and also produce state dependent learning, would enable us to use the state dependent learning paradigm to combine drugs in such a way that they would collectively depress the presumed hyperexcitability of the central nervous system during drug withdrawal and control withdrawal seizures and symptoms. Furthermore, if changes in drugged state are accompanied by changes in brain excitability levels and, as Goldstein et al. (1974, p. 610) have pointed out, "...for narcotics, therefore, as also for alcohol and barbiturates, the principle mechanisms of tolerance and physical dependence have to be sought within the neural elements of the

central nervous system," and specifically changes in excitability levels of nerve cells (Kalant and Kalant, 1971). The presumed changes in neural excitability levels should be sought in the central nervous system, and the effects of change upon changes of brain excitability levels should be determined.

The method for recording changes in brain excitability levels was the conditioning method of Doty, Rutledge, and Larsen (1956) as modified by Nielson, Knight, and Porter (1962). Cats were trained to give foreleg flexion conditioned responses (CRs) to peripheral stimulation (1000 Hz tone) or to direct electrical stimulation of the brain as the conditioned stimulus (CS). When the CR was well established, the excitability of the neural tissue was measured by determining the CS intensity necessary to maintain responses (conditioning threshold); (Doty, Rutledge, and Larsen, 1956; Nielson, Knight, and Porter, 1962).

The general procedure was that cats were habituated to a hammock which allowed free movement of the head and limbs, but restricted gross locomotion. When habituation was complete, and the animals were tolerant of such restraint and remained quiet, hammock training was temporarily discontinued to anesthetize the animals and surgically fit them with pairs of stereotaxically placed bipolar electrodes. The electrodes themselves were made of 27 gauge nichrome wire that was insulated except at stimulating tips that had a 1 mm vertical separation. Four pairs of electrodes were implanted in each cat with four target sites selected from the following brain structures: mesencephalic reticular formation, center median, medial forebrain bundle, lateral hypothalamus, ventromedial hypothalamus, amygdala, hippocampus, caudate nucleus, putamen, medial geniculate body, and lateral geniculate body. When the cats had recovered from this surgery they were re-habituated to the hammock, and when again tolerant of the restraint and remained quiet, avoidance training was begun. The CS was delivered for two seconds and was either a 1000 Hz tone, or the brain was directly stimulated with a train of electrical square wave pulses delivered through the chronically implanted electrodes. The unconditioned stimulus (US) was also a train of electrical square wave pulses, .2 sec in duration that overlapped the CS by 50 msec, that was delivered to the cat's right foreleg through a leg cuff and a grid upon which its leg was placed. The CR was a right foreleg flexion which broke the US circuit and allowed the animal to avoid the US. After the animal had learned to consistently respond to stimulation of one brain area as the CS, it was then trained to give CRs to electrical stimulation to other brain areas or to the tone. When stable CRs were obtained from several brain areas in the same cat, conditioning thresholds were taken. These thresholds were obtained by lowering the intensity of the brain stimulation CS in blocks of five trials until CRs were no longer obtained. Then the intensity of the CS increased in blocks of five trials until CRs again appear. This process is repeated until stable conditioning responses, defined as the stimulus intensity that maintains 50% CRs, are obtained. Such thresholds are stable for as long as two years (Nielson and Davis, 1966). Furthermore, these thresholds are sensitive to changes in neural excitability levels produced by electroconvulsive shock (Nielson, 1968), brain lesions remote from the site of stimulation (Nielson and Davis, 1966), different



drugs and drug dosages (Nielson, Justesen, and Porter, 1968; Pusakulich and Nielson, 1972). In addition, acquisition of these CRs and their conditioning thresholds can be state dependent (Pusakulich and Nielson, 1972).

With the conditioning technique used here, the following changes in brain excitability can be followed, those produced by different drugs and drug dosage levels; those produced during the development of physical dependence upon pentobarbital, those produced by the withdrawal of drugs from animals with state dependent CRs; and those produced by withholding pentobarbital from pentobarbital dependent animals. With this information about the brain excitability changes we believed that we could select a drug or drug combination that would eliminate the animals' withdrawal symptoms. The selection of the drug or drug combination was based upon two empirical considerations. The first was the extent to which one drug could substitute for another based upon the extent to which the substitute drug or drug combinations changed brain conditioning thresholds. The second consideration was the extent to which the animal viewed the substitute drug as producing the same psychological consequences as the addicting drug, i.e., whether the substitute drug maintained a state dependent response. To proceed we derived five hypotheses to be tested:

1. Drugs that are addictive, and maintain state dependent learning can be freely substituted to maintain state dependent learning produced by an ip injection of 15 mg/kg sodium pentobarbital.
2. Drugs that can be substituted to maintain state dependent learning are effective substitutes because they produce the same changes in brain excitability levels as does an ip injection of 15 mg/kg sodium pentobarbital.
3. Drugs that can substitute for an ip injection of 15 mg/kg sodium pentobarbital can, either singly or in combinations, block, retard, or otherwise alter the withdrawal symptoms produced by withholding pentobarbital from pentobarbital dependent cats.
4. Drug combinations will be more effective in eliminating pentobarbital withdrawal symptoms, than will drugs used singly. Furthermore, drug combinations will not have the addictive potential that drugs used singly will.
5. Drug combinations that can substitute for pentobarbital and block pentobarbital withdrawal seizures are not themselves addictive.

To test the first hypothesis two experiments were devised. The first experiment was conducted to determine what dosages of some drugs that produce state dependent learning equivalent to each other and also equivalent to 15 mg/kg of pentobarbital, in the normal non-addicted cat, in their ability to change brain excitability levels as measured by changes in the conditioning threshold. With this information, the drug and dosage levels as a basis for substitution based upon the changes in brain CR thresholds were established. In the second experiment we determined the extent that the drugs were psychologically equal in that they would maintain state dependent CRs. Cats were trained while under the influence of 15 mg/kg pentobarbital so that their

CRs were state dependent. Then, the substitute drugs were given singly and in combinations, in dosages that were found in the first experiment to produce the same CR threshold effect as 12.5 mg/kg pentobarbital, were substituted for the pentobarbital to determine whether they would maintain the pentobarbital dependent CRs. (The cats were trained under a dosage level of 12.5 mg/kg because this dosage level produces the same state as 15.0 mg/kg (Pusakulich and Nielson, 1972)).

Experiment I. Experiment I was designed to determine which drugs, and at what dosages, and for what period of time, produced changes in brain CR thresholds comparable to those produced by an intraperitoneal injection of 12-15 mg/kg sodium pentobarbital. This was accomplished by stereotaxically placing bipolar electrodes in a variety of brain areas of cats, but especially in the hippocampus, medial geniculate body, mesencephalic reticular formation and the caudate nucleus. When the cats had recovered from this surgery they were habituated to a conditioning apparatus, which allowed movement of the head and limbs but limited gross locomotion, until they became tolerant of this restraint and remained quiet. Then, avoidance conditioning training was started. The conditioned stimulus (CS) was a train of electrical square wave pulses delivered to a particular brain site, through the chronically implanted electrodes, for 2 sec. The unconditioned stimulus (US) was also a train of electrical square wave pulses, .2 sec in duration and overlapping the CS by 50 msec, that was delivered to the cat's right foreleg through a leg cuff and a grid upon which its leg is placed. The conditioned response (CR) was a flexion of the right foreleg which broke the US circuit and allowed the animal to avoid the US. When the animal had learned to give a high number of CRs, the same training procedure was carried out with electrical stimulation of another brain site as the CS. Each cat was trained to give CRs to electrical stimulation of at least two different brain sites.

When avoidance training was complete the threshold of each brain site was determined. This was done by lowering the intensity of the CS in blocks of five trials until no CRs were obtained. The intensity of the CS was then gradually increased until a high level of performance was again obtained. This process was repeated several times a day for several days until stable thresholds, defined as the CS intensity that gives 50% CRs, had been determined. After stable thresholds had been determined, the experimental animal was given a low drug dose and thresholds were again determined. If there were no identifiable threshold changes produced by the drug, the animal was returned to its home cage. The following day a larger drug dosage was given and thresholds again taken. The drug dosage was progressively increased until the animal was sufficiently intoxicated that it could not perform or CR could no longer be obtained. When a given dosage of a drug resulted in a shift in brain thresholds, the animal was tested two, four and eight hours later or until the drug wore off and the thresholds returned to normal. After thus determining the drug effect and its time course upon the brain thresholds, another drug dosage level was given and the duration of effect determined. This continued until a range of dosage levels had been given so that the smallest dosage had no effect upon the threshold while the largest dose completely abolished the CRs. When a dose response curve was thus determined

in one cat it was verified in other cats that had never received that drug before. The same procedure was used when different drug combinations were investigated.

The effects of the various drugs and drug dosages are summarized in Figures 1-12. Each of the curves in figures is based upon the data obtained from at least three cats with that electrode placement and that drug, and each figure is based upon at least five cats. The effects of various drug dosages upon the conditioning threshold of the caudate nucleus is summarized for paraldehyde in Figure 1, for librium in Figure 2, for chloral hydrate in Figure 3, for meprobamate in Figure 4, and for ethyl alcohol in Figure 5. Similar dose response curves were obtained for these drugs upon the conditioning thresholds of the geniculate and the mesencephalic reticular formation. The only differences in the drug effects upon the geniculate and the caudate nucleus were found with librium and meprobamate. The effects of these two drugs upon the excitability level of the geniculate is shown in Figure 6 for librium, and Figure 7 for meprobamate. The differences in the drug effects upon the caudate nucleus and the geniculate and directly compared in Figure 8 for librium and Figure 9 for meprobamate. Inspection of these figures shows that there were differences in CR thresholds of these two brain structures only with the intermediate dosage levels, and these differences showed the caudate nucleus to be slightly more sensitive to the drugs than was the medial geniculate body. There were no other differences in the drug effect between the caudate nucleus and the medial geniculate body. The drug effects upon the mesencephalic reticular formation were identical to those upon the caudate nucleus and are not reproduced here.

The different drug dosage combinations were next determined. Because of the similarity of the drug effects upon the three brain structures, the drug combination effects are detailed only for the caudate nucleus. Figures 10 and 11 show the effects of different combinations of librium and meprobamate upon the conditioning thresholds of the caudate nucleus. Figure 10 compares the low dosage levels and shows that the combination of 5 mg/kg librium, which singly produced only a transient effect upon brain excitability, and 25 mg/kg of meprobamate, which singly had no effect upon brain excitability, produced a small, but very long lasting depression of brain excitability. Figure 11 shows the effect of larger dosages of the librium-meprobamate combination. A single dose of meprobamate of 50 mg/kg decreased the excitability of the caudate nucleus for eight hours when given alone. However, when this dose of meprobamate was combined with librium of 10 mg/kg, which singly had no effect upon brain excitability levels, produced a profound depression of the excitability level of the caudate nucleus such that the conditioned responses were lost for over eight hours. We now believe that any combinations of paraldehyde, librium, chloral hydrate, meprobamate, and ethyl alcohol, where the combination is one half of the dosage level that abolished the CRs for any drug is combined with one half of the dosage level of any other drug that abolished the conditioned response the two drugs will combine and abolish the CR for long periods of time. The potentiation of drug effects is great when its depression upon the conditioning thresholds is measured, but the greatest effect of the drug potentiation is upon prolonging the depression of brain excitability. Thus, the combination of these drugs



produces a depression of CRs for four to six times as long as does a single dose of a single drug given in twice the amount of any of the drug given in a drug combination.

To emphasize the nearly identical effects of the drugs effects upon the caudate nucleus and the mesencephalic reticular formation the responses of these two structures to the meprobamate-librium drug combinations is shown in Figure 12. The data for the figures were taken from cats from which CR thresholds were taken from both the caudate nucleus and the mesencephalic reticular formation, so that it represents data within cats. Similar comparisons between cats that had CR thresholds from only one or the other cites showed the same thing. The drugs all effected the caudate nucleus and the mesencephalic reticular formation in the same way. The identical nature of the drug effects upon these two structures is emphasized here because we find a dissociation of the drug effects on these two structures as the cat becomes addicted to pentobarbital.

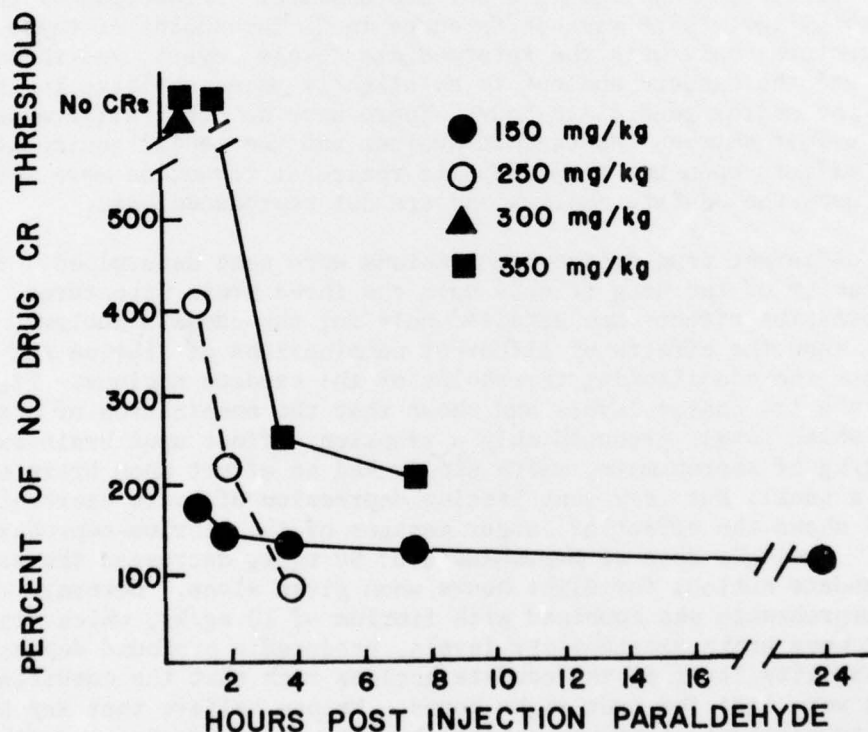


Figure 1. Changes in conditioned response thresholds of the caudate nucleus as a function of dosage level and time since administration.

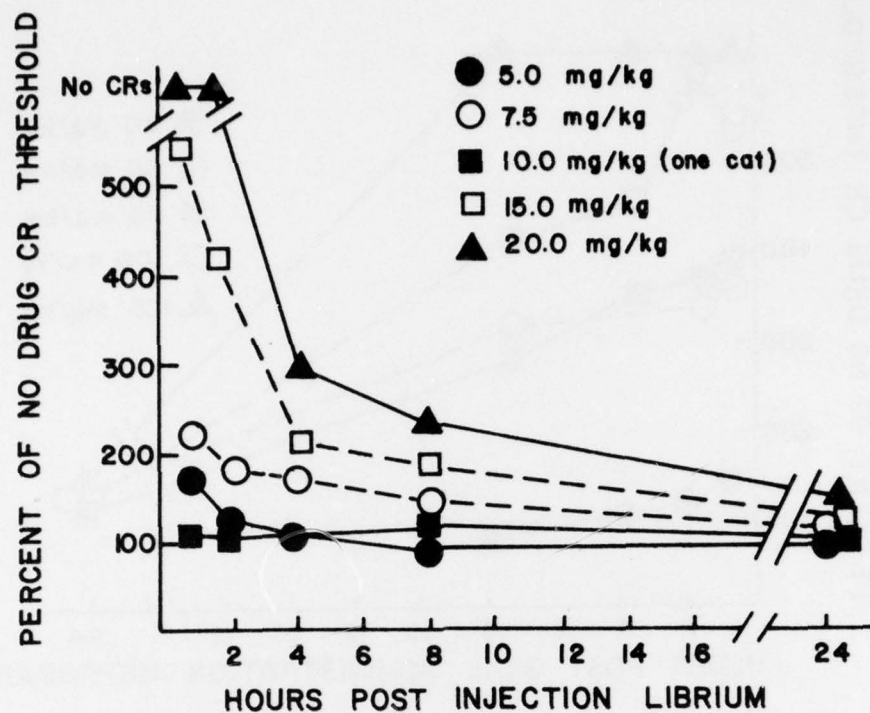


Figure 2. Changes in conditioned response thresholds of the caudate nucleus as a function of dosage level and time since administration.

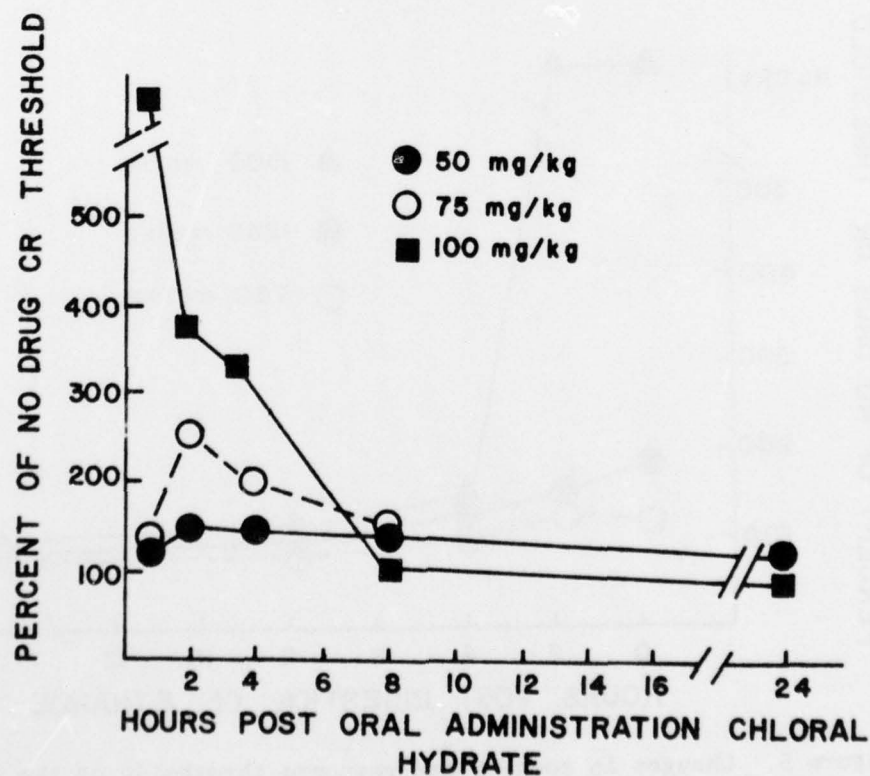


Figure 3. Changes in conditioned response thresholds of the caudate nucleus as a function of dosage level and time since administration.

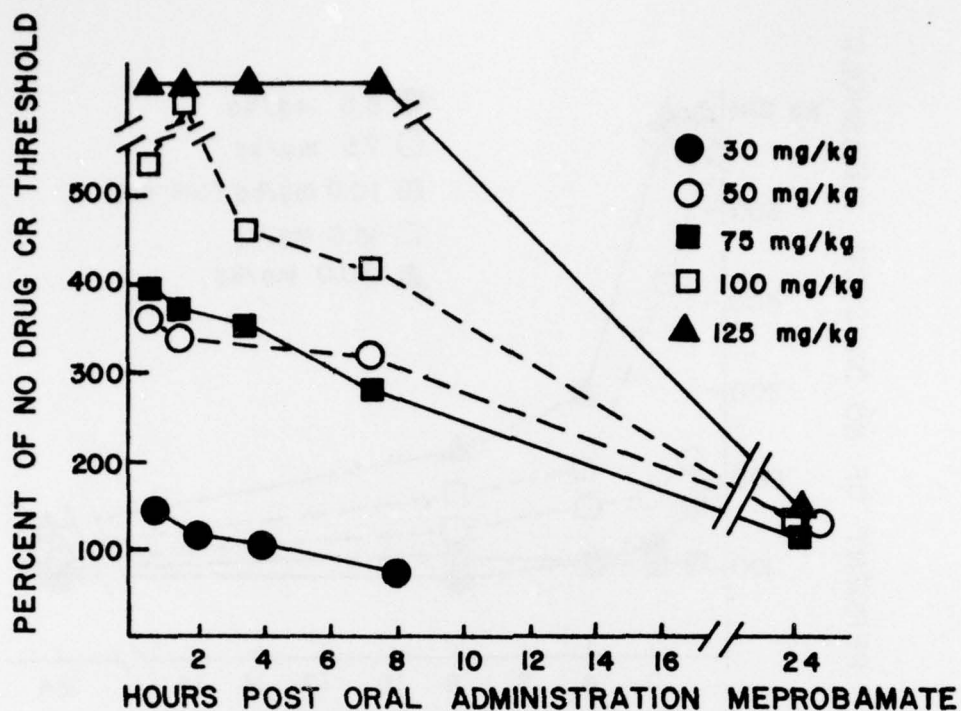


Figure 4. Changes in conditioned response thresholds of the caudate nucleus as a function of dosage level and time since administration.

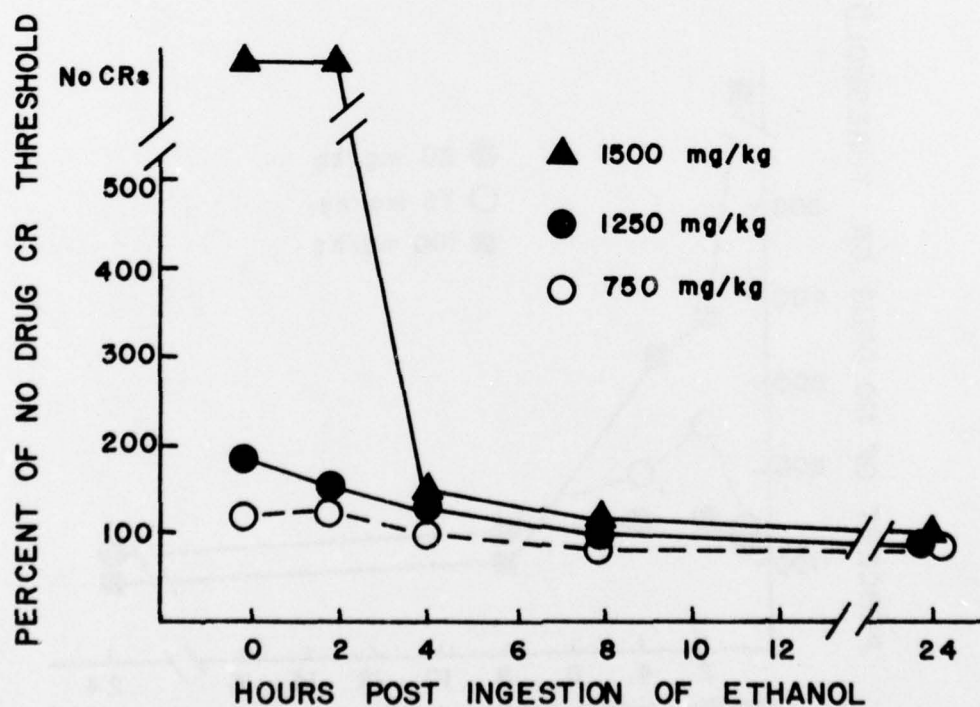


Figure 5. Changes in conditioned response thresholds of the caudate nucleus as a function of dosage level and time since administration.



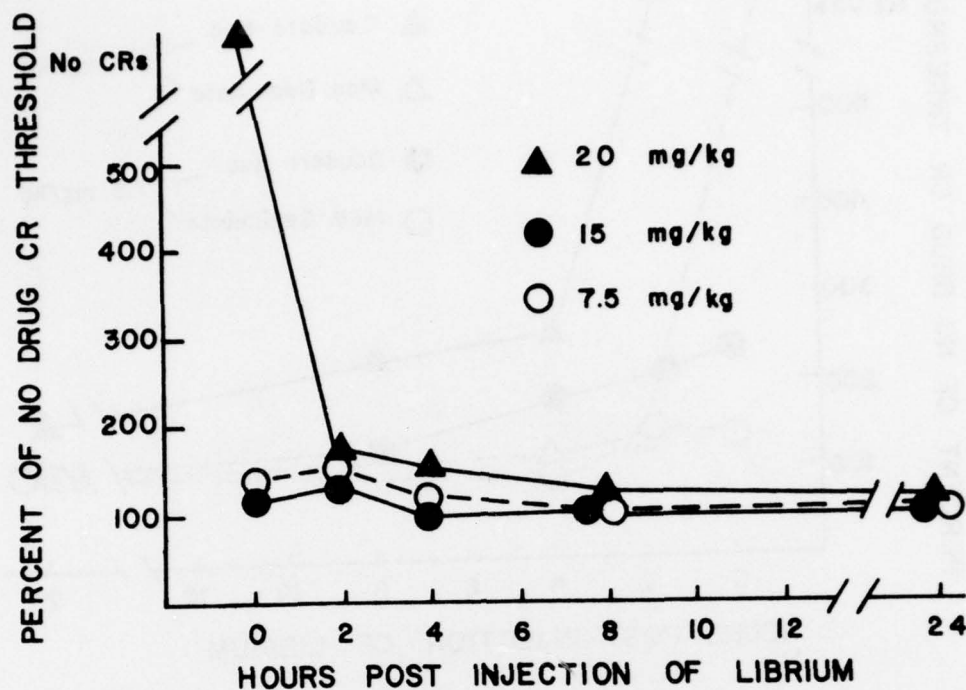


Figure 6. Changes in conditioned response thresholds of the medial geniculate as a function of dosage level and time since administration.

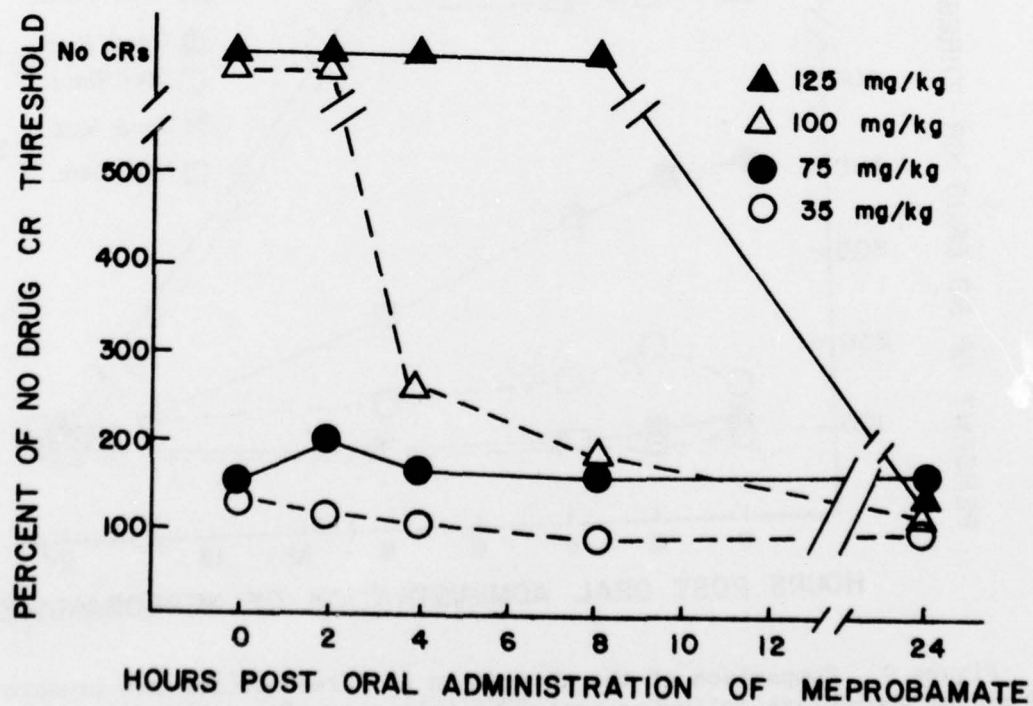


Figure 7. Changes in conditioned response threshold of the medial geniculate as a function of dosage level and time since administration.

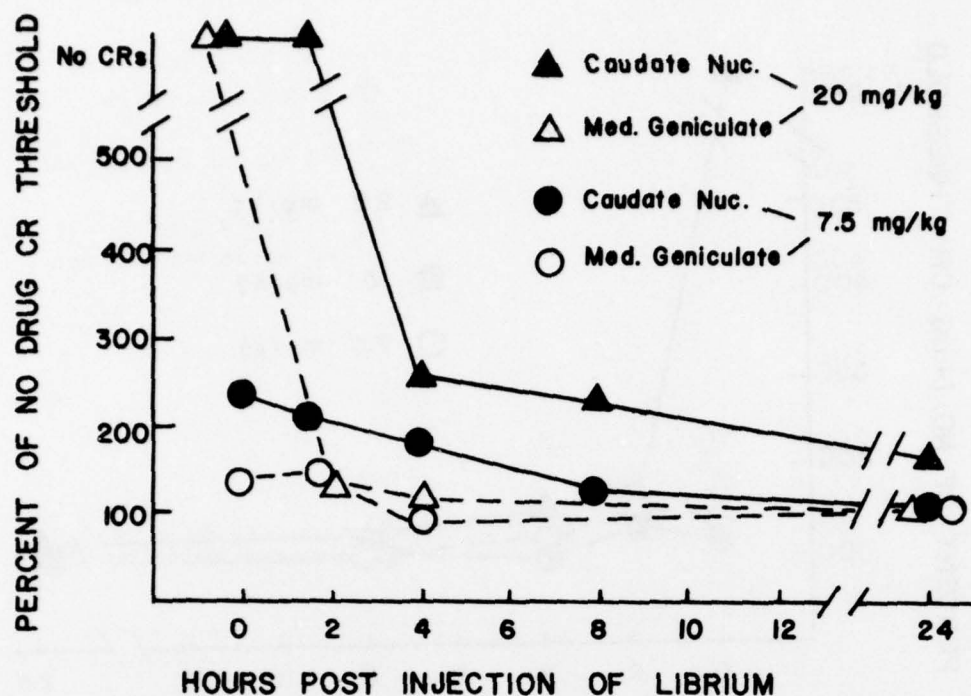


Figure 8. Comparison of the effects of Librium (20 mg/kg and 7.5 mg/kg) upon the conditioned response thresholds of the caudate nucleus and the medial geniculate.

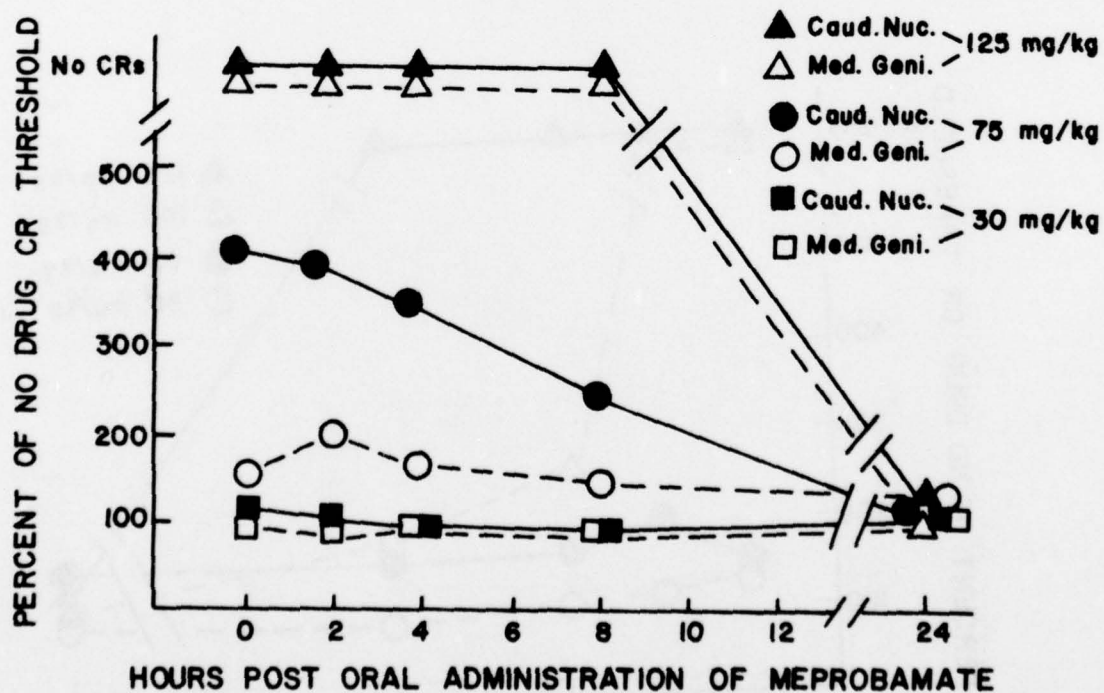


Figure 9. Comparison of the changes in CR threshold for the caudate nucleus and medial geniculate following oral administration of meprobamate.

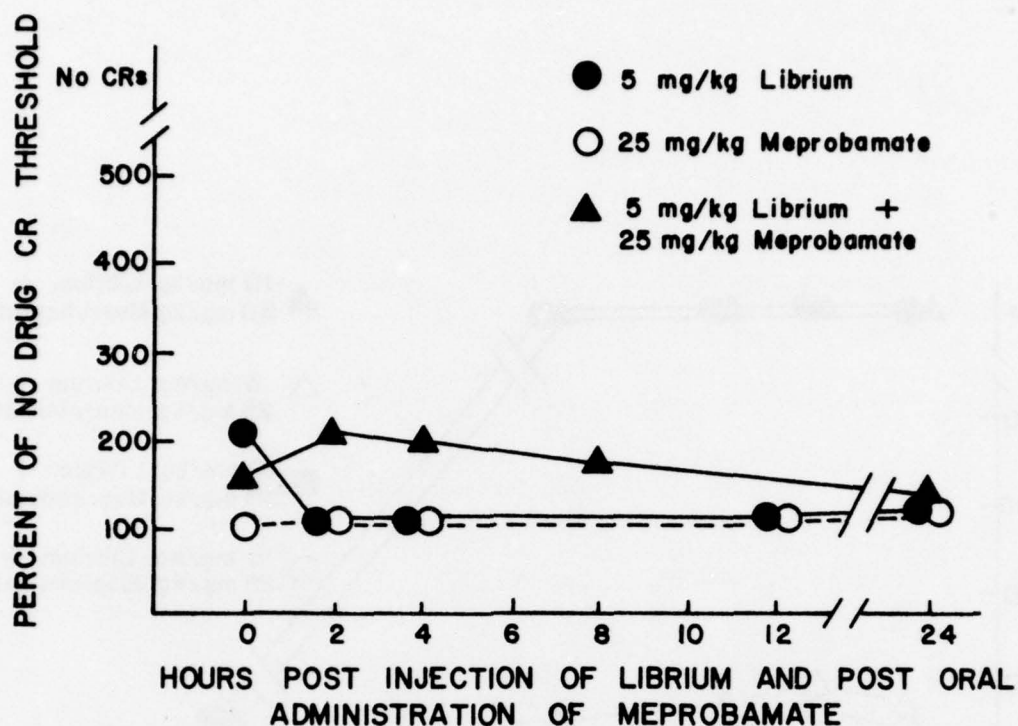


Figure 10. Effects of Librium (5 mg/kg) and Meprobamate (25 mg/kg) administered singly or in combination upon the conditioned response threshold of the caudate nucleus.

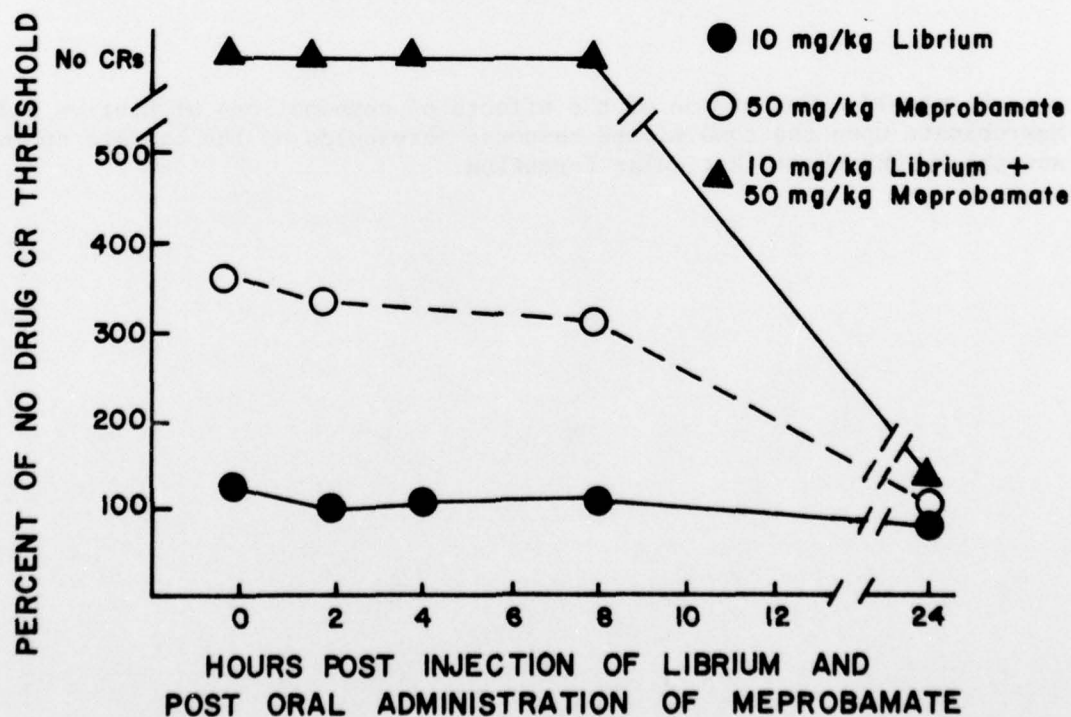


Figure 11. Effect of Librium (10 mg/kg) and Meprobamate (50 mg/kg) administered singly or in combination upon the conditioned response thresholds of the caudate nucleus.

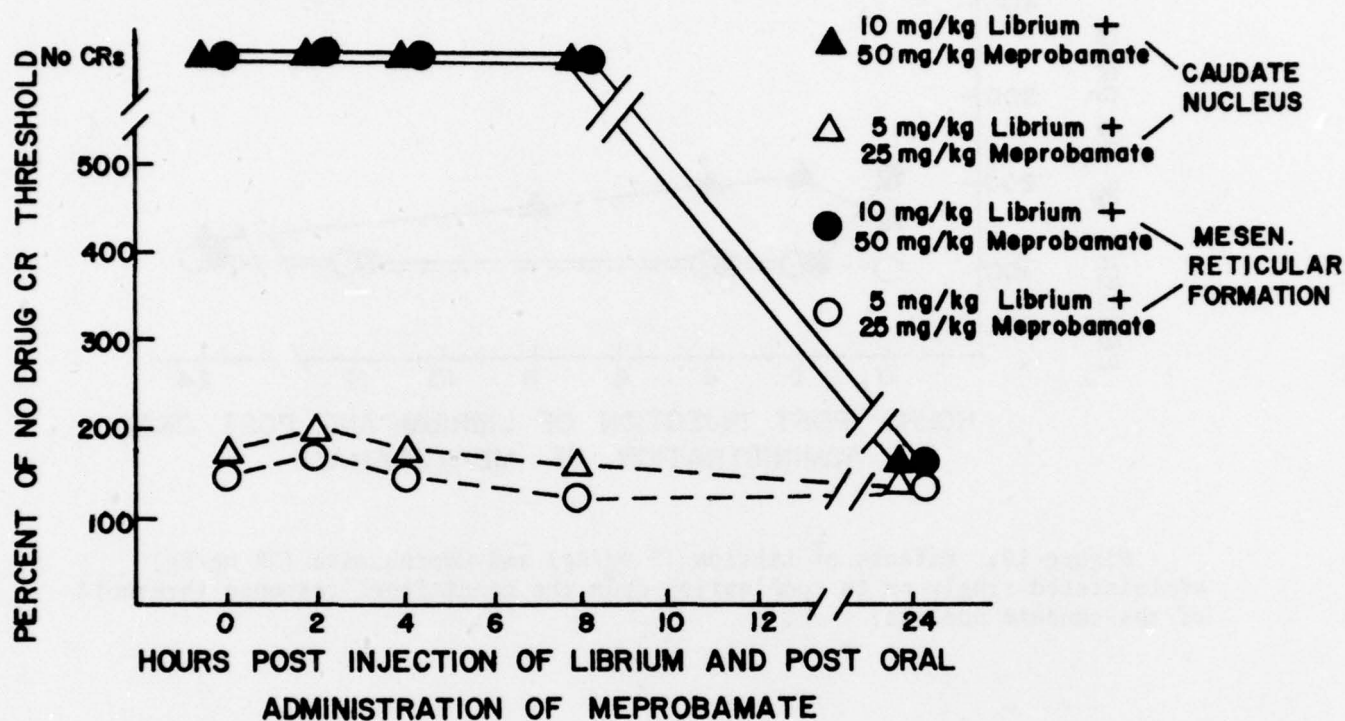


Figure 12. Comparison of the effects of combinations of Librium and Meprobamate upon the conditioned response thresholds of the caudate nucleus and the Mesencephalic Reticular Formation.



Experiment II. Drug substitution. In this experiment we determine the psychological equivalence of drugs by determining the extent to which a cat views a variety of dosage levels given singly and in combinations, of paraldehyde, librium, chloral hydrate, and meprobamate as producing the same drugged state as that produced by an ip injection of 15 mg/kg of pentobarbital. We can do this because these drugs all produce state dependent learning, and the maintenance of the response is dependent upon the maintenance of the drugged or non-drugged state that existed at the time of response acquisition. If both these conditions are met, the response is said to be state dependent.

The specific training procedure is identical to that of the first experiment. The general training procedure differs from the first experiment only in that these animals begin each training session after receiving an ip injection of 12.5 to 15.0 mg/kg pentobarbital. Because all training is conducted while the cats were in the drugged state the CRs were state dependent.

To put the results of the drug substitution tests in perspective, the effects of various dosage levels of pentobarbital upon the training thresholds and percent CRs of drugged trained and non-drugged (normal) trained cats is shown in Figures 13 and 14. These figures show that as the dosage level of pentobarbital changed away from the training state there was a progressive loss of CRs and an increase in CR threshold. Thus giving normally trained animals (those in experiments I and IV) increasing doses of pentobarbital progressively elevates the CR threshold and decreases the percentage of CRs. Nearly the reverse was true for those cats trained in the drugged state produced by 12.5 mg/kg of pentobarbital. For these cats the thresholds increased as the dosage level of pentobarbital was decreased. Similarly, the percentage of CRs decreased as dosage level of pentobarbital decreased until CRs were lost. Thus we can conclude that CR thresholds are a function of the animals training state, and deviations from the training state produce elevations in CR thresholds, a reduction and finally a loss of CRs. We can conclude that the CR thresholds are a function of experience in a state and not only the pharmacological action of the drug alone.

The dissociative dose of pentobarbital for the normally trained cats was 12.5 mg/kg which was the training dose for the drugged trained cats. The results from our drug substitution tests show that in each instance, the dissociative dose of the substitute drug, the dosage level that abolished the CRs in experiment I, was an adequate substitute for 12.5 mg/kg pentobarbital. Paraldehyde at 300 and 350 mg/kg, chloral hydrate at 100 mg/kg, librium at 20 mg/kg and meprobamate at 100 mg/kg all substituted for 12.5 mg/kg of pentobarbital and maintained state dependent responding. Ethyl alcohol was not tested because these cats were not fitted with tubes so that alcohol could be administered without the cats vomiting it up. Smaller drug dosage levels of these drugs that were not dissociative and that did not abolish CRs in experiment I, did not substitute for pentobarbital and maintain the CRs. Thus the adequate substitute dose in this experiment was the dissociative dose found in experiment I.

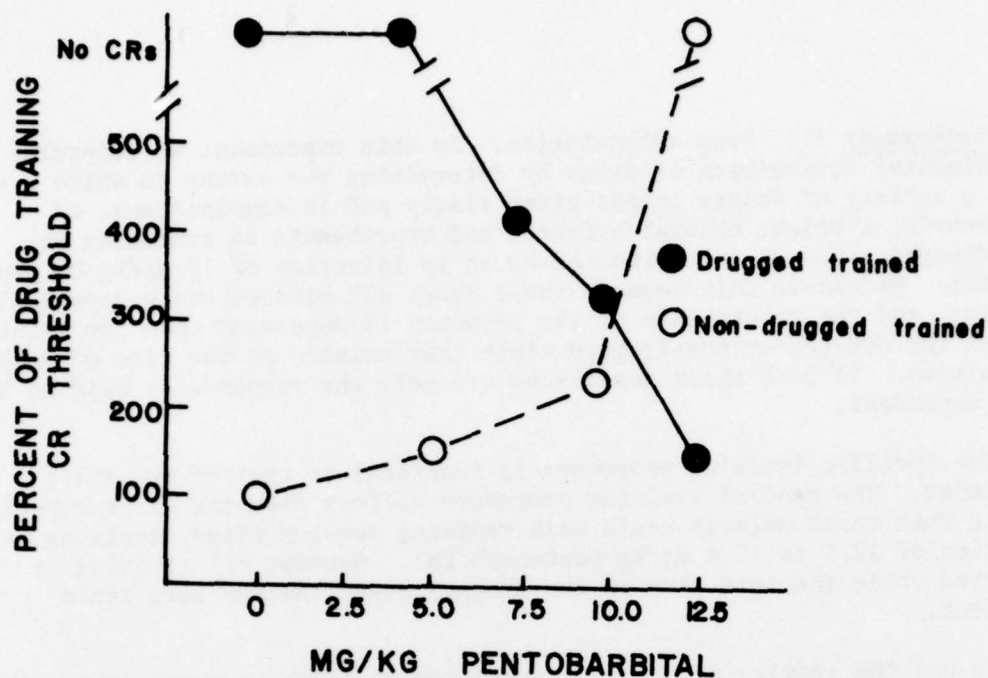


Figure 13. Comparison of the effects of variation in the dosage levels of pentobarbital upon the training threshold of drugged and nondrugged trained cats.

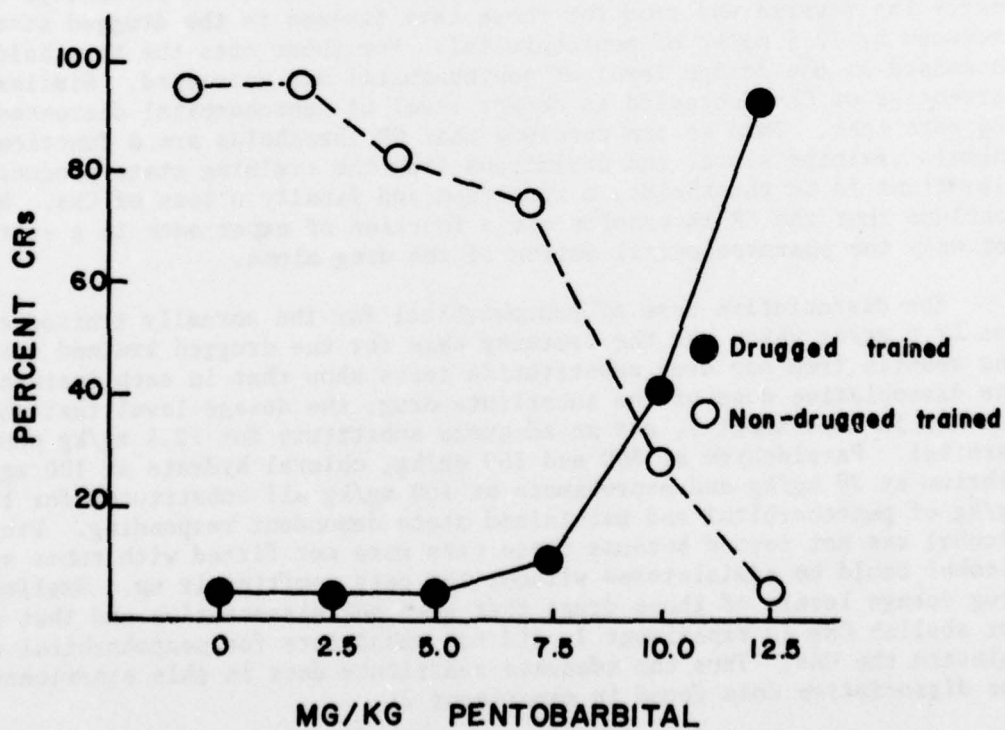


Figure 14. Comparison of the effects of various dosage levels of pentobarbital upon the percent CRs of cats trained in the drugged (12.5 mg/kg) state and the nondrugged (normal) state.



The different substitute drugs had somewhat different side effects upon the cats. Paraldehyde (300 mg/kg) produced a cat that early in the training session seemed much more sedated than with 12.5 mg/kg pentobarbital, but as testing continued these cats, unlike those in the first experiment that were normally trained and received the same dosage level, seemed to experience a general distress. However, they continued to give good CRs throughout the session. When the cats received chloral hydrate (100 mg/kg) they were calm and quiet throughout the sessions. Their CRs were good but they were not as good as they were with pentobarbital. Librium (20 mg/kg) produced cats that were jittery and agitated and seemed very nervous and restless. Their CRs were good and remain so. Meprobamate (100 mg/kg) produced a cat that was calm and seemed to be less sedated than with pentobarbital. The CRs were slow but full. The drug combination of librium (10 mg/kg) and meprobamate (50 mg/kg) which also produced dissociation of the CRs in experiment I also substituted for the pentobarbital. This drug combination produced cats that were very difficult to handle. They seemed more jittery and agitated than when they received librium alone. Their CRs were good, however. A combination of chloral hydrate and meprobamate, made up of half the dissociative dose of each (chloral hydrate 50 mg/kg and meprobamate 50 mg/kg) was also tested. These drugs separately had produced cats that were calm and well behaved. This drug combination substituted for pentobarbital in that the cats gave better than 50 percent CRs, although the CRs were poor in quality. The cats themselves were very calm, easy to handle and seemed alert. Thus a drug combination, mixed 1/2 and 1/2 of the dissociative doses of the respective drugs can substitute for 12.5 mg/kg pentobarbital.

Drug	Dissociative Dose for Normally Trained Cats Experiment Dose mg/kg	% Pentobarbital Threshold of Drugged Trained Cats of Experiment II	Quality of the CRs	Assessment of the animal's mood
Paraldehyde	300	90	Good	Some dis- tress
Chloral hydrate	100	90	Good	Calm
Librium	20	140	Good	Jittery and agitated
Meprobamate	100	50	Fair (slow)	Calm
Librium and meprobamate	10 and 50	120	Good	Very agitated
Chloral hydrate and meprobamate	10 and 50	25	Poor	Calm and seemed alert

Table 1. The drugs and drug combinations and dosage levels which maintained pentobarbital dependent CRs. Also included is a comparison of their effect upon the conditioning thresholds of animals with placements in the caudate nucleus and with pentobarbital dependent CRs, and a description of the quality of the CRs and the animal's mood. Each value is based upon the data from at least three cats.

Threshold determinations taken for each of the drugs and drug combinations is shown in Table 1. The thresholds are presented as percentage of pentobarbital state (12.5 mg/kg). CR thresholds: Most of the thresholds were fairly close to the CR thresholds obtained in the pentobarbital state. However, the chloral hydrate meprobamate combination produced thresholds that were considerably lower than the pentobarbital state threshold. It should also be pointed out that this deviation in threshold was of the greatest magnitude and also produced the poorest CRs. It is different from the expected changes in that all previous deviations from the training state have produced increased CR thresholds. Except for librium, all the other substitute drugs have produced decreases in CR thresholds. Altogether 22 cats were used in experiments I and II, and the entries for each of the data points in Figures 1-14 and Table 1 are based up at least three and usually five animals. With repeated testing of the same animals, with a variety of drugs that produce the same effects and are cross tolerant, it would appear that tolerance would develop. However, these dose response curves were always stable. The CR thresholds without drugs were stable for individual animals throughout the experiment. In addition, the dose response curves remained stable. We did not see a single elevation or decrease in CR threshold that could be interpreted as tolerance. With repeated doses of the same drug the same CR thresholds, and dose response curves were obtained. We have seen no evidence, or found no evidence for any hypothetical construct that could even be remotely labeled as "neural tolerance." A fact that did emerge from these experiments is that the psychological equivalence of states is not determined by the brain excitability shifts produced by the respective drugs. Rather, brain excitability shifts produced by pentobarbital is partly a function of the animal's experience with the drugged state.

The first hypothesis: "Drugs that are addictive, and maintain state dependent learning, can be freely substituted to maintain state dependent learning produced by an ip injection of 12.5 mg/kg (the same state as 15.0 mg/kg) of pentobarbital" was confirmed. The second hypothesis: "Drugs that can be substituted to maintain state dependent learning are effective substitutes because they produce the same changes in brain excitability levels as does an ip injection of 15 mg/kg pentobarbital" was not confirmed. Inspection of Table 1 shows that paraldehyde and chloral hydrate produced nearly the same conditioning thresholds as did the pentobarbital. Librium produced elevated CR thresholds, meprobamate greatly reduced them and they were further reduced with meprobamate in combination with chloral hydrate. Thus, it appears, that the basis for the effectiveness of drug substitutions in maintaining state dependent CRs is not because they produce the same changes in brain excitability. In fact it now seems unlikely, with its ability to effectively substitute for that drug, that matches in brain excitability of drugged trained cats has anything to do with the ability of one drug to substitute for another.

The third and fourth hypotheses were tested together. The third hypothesis: "Drugs that can substitute for an ip injection of 15 mg/kg sodium pentobarbital can, either singly or in combinations, block retard, or otherwise alter the withdrawal symptoms produced by withholding pentobarbital from pentobarbital dependent cats. And the fourth hypothesis: "Drug combinations will be more effective in eliminating withdrawal symptoms, than will

drugs used singly; furthermore, drug combinations will not have the addictive potential that drugs used singly will," was tested with a variety of experiments, some of which were designed to develop means or ways of testing the hypothesis. The fourth experiment was designed to develop a method to produce physical dependence to pentobarbital in cats and at the same time be able to follow the brain excitability changes associated with the development of dependence and withdrawal symptoms and seizures.

#### Experiment IV: Addition of Cats to Pentobarbital

Method and procedure. Cats were surgically implanted with bipolar electrodes in a variety of subcortical areas, with emphasis upon the caudate nucleus and the mesencephalic reticular formation. When they recovered from this surgery they were habituated to a hammock and conditioned responses established to electrical stimulation of subcortical areas. The conditioning procedure and apparatus were identical to those previously described, except for two variations. In addition to establishing CRs and then determining the CR thresholds, kindling seizures were established in some of the cats and the seizure thresholds determined. In addition, thresholds for any forced movements were determined and followed throughout the experiment. After the cats were conditioned, CR, forced movement, and seizure thresholds determined, they were made physically dependent upon pentobarbital. The addiction procedure is one that we have developed. Each cat is given a single ip injection of 30 mg/kg pentobarbital for 10 days. A withdrawal probe was then given where pentobarbital was withheld and CR, forced movement and seizure thresholds were determined for the next three days. At the end of the three days withdrawal probe the cats were given 45 mg/kg pentobarbital in two ip injections of pentobarbital for 10 days. The first ip injection is 30 mg/kg followed 7-10 hours later with a second ip injection of 15 mg/kg. At the end of this 10 day period another three day withdrawal probe was given and CR, forced movement, and seizure thresholds were taken. A third 10 day addiction period followed the second withdrawal probe during which the cats received 60 mg/kg pentobarbital in two ip injections of 40 mg/kg followed 7-10 hours later by a 20 mg/kg injection. At the end of this 10 day addiction period there was another withdrawal probe of three days followed by a fourth addiction period where the cats received 70 mg/kg per day for 10 days with the first ip injection of 40 mg/kg followed in 7-10 hours by a second ip injection of 30 mg/kg. This addiction period was repeated and followed by withdrawal of all barbiturates.

The results of addiction and withdrawal upon brain excitability changes are shown in Figure 15 for one cat, and in Table II for the remaining cats that have been through the addiction sequence. The only brain area that has shown permanent shifts in excitability as a consequence of addiction is the caudate nucleus and this was a decrease in excitability as indicated by elevated CR thresholds. Other brain areas such as the hippocampus, medial geniculate body, center median, parafascicularis, and mesencephalic reticular formation show some decrease in excitability, as indicated by increased CR thresholds, early in the addiction sequence but they return to normal or near normal as the addiction sequence continues.



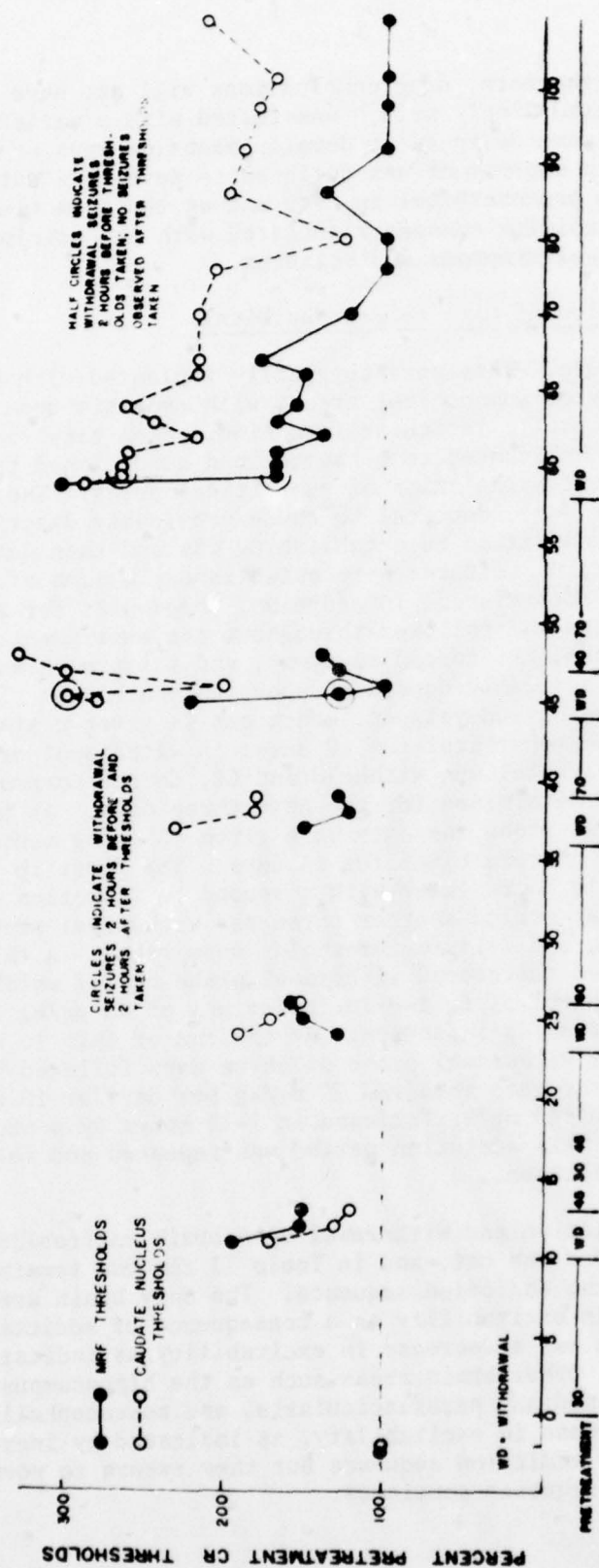


Figure 15. Sequence of conditioning threshold changes for the caudate nucleus and the mesencephalic reticular formation during the development of physical dependence and withdrawal from pentobarbital. Baseline is in days of treatment, daily treatment dosage levels of pentobarbital, and withdrawal probes and periods.

CR thresholds: Normal, during withdrawal probes, or percent CRs to tone CS

Cat	CS Site	Normal	After 30 mg/kg	After 45 mg/kg	After 70 mg/kg
A-1	Mesoreticulum Tone	.027 92	.045 80	.065 43	.035 80
A-2	Caudate Kindling seizure	.11 .09	.14 .10	.16 .09	.17 .09
A-4	Mesoreticulum Hippocampus	.035 .11	.035 .10	.035 .10	.035 .10
A-5	Mesoreticulum Caudate	.018 .10	.035 .17	.023 .19	.028 .15
A-6	Medial Geniculate Tone	.13 80	No CR 21	.20+ 20	.12 63
					.035 .037 .270 .150 29 32

Table II. Thresholds during withdrawal probes following 10 consecutive day administration of pentobarbital of 25 mg/kg/day, 30 mg/kg/day, 45 mg/kg/day, and 70 mg/kg day.

+Quality of responding was very poor.

Caudate threshold: .11 mA  
MRF threshold: .020 mA

	<u>30 mg/kg pentobarbital</u>		
	<u>24</u>	<u>48</u>	<u>72</u>
Caudate	.17	.14	.12
MRF	.035	.028	.027

Withdrawal probe beginning at day 11 after 10 days at 30 mg/kg pentobarbital (days 1-13).

	<u>45 mg/kg pentobarbital</u>		
	<u>24</u>	<u>48</u>	<u>72</u>
Caudate	.19	.17	.17
MRF	.023	.028	.028

Withdrawal probe after 10 days at 45 mg/kg pentobarbital (days 14-26).

	<u>60 mg/kg pentobarbital</u>		
	<u>24</u>	<u>48</u>	<u>72</u>
Caudate	.24	.17	.18
MRF	.025	.022	.023

Withdrawal probe after 10 days at 60 mg/kg pentobarbital (days 27-39).

	<u>70 mg/kg pentobarbital</u>				
	<u>24</u>	<u>36</u>	<u>48</u>	<u>72</u>	<u>96</u>
Caudate	.28	.30	.21	.30	.32
MRF	.04	.024	.018	.023	.025

Withdrawal probe after 5 days at 70 mg/kg pentobarbital (days 40-48).

	<u>70 mg/kg pentobarbital</u>						
	<u>24</u>	<u>36</u>	<u>48</u>	<u>72</u>	<u>96</u>	<u>120</u>	<u>144</u>
Caudate	.32	.29	.29	.29	.25	.27	.29
MRF	.055	.030	.030	.030	.025	.030	.028

Withdrawal probe after 1 day at 40 mg/kg pentobarbital plus 11 days at 70 mg/kg pentobarbital (days 48- ).

Table IIa. Protocol for Cat #S-3 whose CR thresholds are plotted in Figure 15.



During drug withdrawal, withdrawal seizures have been recorded immediately before and after conditioning thresholds have been taken. Yet no reliable changes in brain excitability levels were noted that could be attributed to drug withdrawal. There were no changes in the thresholds for either the kindling seizure, forced movement, or conditioning thresholds to support, or even hint, that the central nervous system was hyper-excitabile during drug withdrawal. It seems to us that if the central nervous system is truly hyper-excitabile during drug withdrawal it should have been evident when it was being stimulated directly in some of these neural structures.

Another point of interest from Figure 15 is that the dissociation between the caudate nucleus and the reticular formation is analogous to the dissociation between neural systems seen following ablation of the frontal cortex in cats. In that experiment, Nielson and Davis (1966) found that frontal ablation produced a decrease in the CR thresholds of the basal forebrain sleep inducing area, a transient increase in the CR thresholds of the caudate nucleus, no change in the CR thresholds of the classical sensory relay nuclei of the thalamus, but a permanent increase in the CR thresholds of the mesencephalic reticulum. Thus, addiction to pentobarbital produces changes in the CR thresholds of brain areas in an analogous fashion to those produced by brain ablations. A final point of interest is the poor CR responding to tone seen during withdrawal in some animals, which may be indicative of a reduced responsiveness to peripheral stimulation.

#### Experiment V: Effects of L-Dopa on Thresholds of Caudate Nucleus

Since the only structure of the brain we stimulated which showed consistent and permanent changes in conditioning thresholds, as a consequence of addiction to pentobarbital, was the caudate nucleus, and since this structure is particularly high in dopamine, we investigated the effects administration of l-dopa had upon the thresholds of this structure in normal and previously addicted cats.

Six cats that had been trained to give conditioned responses both to the caudate nucleus and the reticular formation were selected for the experiment. Two of the cats had been previously addicted to pentobarbital, and four cats that had not been addicted to pentobarbital were selected as the subjects. The four non-addicted cats had previously served as subjects in experiment I, but had not been given any drugs for one month prior to receiving injections of l-dopa. One of the previously addicted cats was the one whose conditioning thresholds during the addiction are described in Figure 1. The l-dopa was given orally in the dose of 35 mg/kg to all the cats. The procedure used was the same as described in experiment I.

The effects of 35 mg/kg l-dopa upon the conditioning thresholds of the caudate nucleus and the reticular formation for normal and previously pentobarbital dependent cats is shown in Figure 16. There are three major points to be made. The first is that the effect of l-dopa upon the conditioning thresholds of both the caudate nucleus and the reticular formation of the nonaddicted (normal) cats is nearly identical. The second is that the dissociation of the caudate nucleus and the reticular formation of the previously addicted cat is clearly seen in their response to l-dopa. The reticular

formation response of the previously addicted animals is like the reticular formation response of the normal animal, while the caudate response to l-dopa in the previously addicted animal is markedly different. The third finding of note shown in Figure 16 is that the caudate nucleus of previously addicted animals appears to be biphasically sensitive to dopamine. One hour after l-dopa administration, the conditioning threshold of the caudate nucleus is sufficiently elevated that CRs could not be elicited. Three hours after l-dopa, the caudate nucleus thresholds have returned to their post-withdrawal level, and six hours later, the conditioning thresholds have dropped below the post-withdrawal level and are approaching their pre-addiction level. Twenty-four hours later the conditioning thresholds of the previously addicted animals have returned to their post-withdrawal level.

It is not clear whether the fact that l-dopa abolished the CRs of these animals, one hour after administration of l-dopa, represents an acquired supersensitivity to it, or merely reflects the permanent shift in baseline, since the post-withdrawal threshold is 300 percent above the pre-addiction level. An additional increase of 200 percent in the conditioning thresholds, produced by the l-dopa, may have increased the threshold sufficiently to produce a new state. Thus, the effects of the l-dopa may simply have added to the previous baseline shift produced by the addiction to produce the new state. The behavior of the previously addicted animals offers no real cues as to whether they are supersensitive to dopamine or not, since their behavior was not noticeably different from the normal animals, one and three hours after l-dopa. Typically, their eyes were dilated, thick spittle dripped from their mouths, and they sometimes defecated. They were quite difficult to handle in the hammock and they were sensitive to footshock. For the normal animals their behavior seemed to be back to normal after six hours, although they still seemed a little sensitive to footshock. For the previously addicted animal, six hours after l-dopa, the thresholds of the caudate were dropping below the post-addiction level, and the animals were now more easily handled and seemed friendlier, although they too were still more sensitive to the footshock. The behavior responses, pupillary dilation, salivation, and defecation, elicited from all of the animals by l-dopa have also been seen in cats that will press a bar for electrical stimulation of the caudate. Caudatal self-stimulation has been described as producing seizure-like behavior (Nielson, Doty, and Rutledge, 1958), and EEG signs of seizure-like activity accompany self-stimulation (Porter, Conrad, and Brady, 1959). However, all of the animals seemed more sensitive to peripheral stimulation as a result of l-dopa administration. Nevertheless, the impression remains that the previously addicted cats became easier to handle, and seemed more "normal" when their caudate thresholds approached their pre-addiction threshold. It remains to be seen whether prolonged administration of l-dopa would eventually return the caudate nucleus threshold to normal and whether this would prevent withdrawal seizures.

Since cats that had been previously addicted to pentobarbital seemed more normal, were easier to handle when their caudate thresholds approached their pre-addiction threshold, the effect of amphetamine upon the CR thresholds of the caudate nucleus of the non-addicted cats was investigated. Previously addicted cats were not used because none of them were available at the time. Amphetamine was used because of its effects upon the release of dopamine

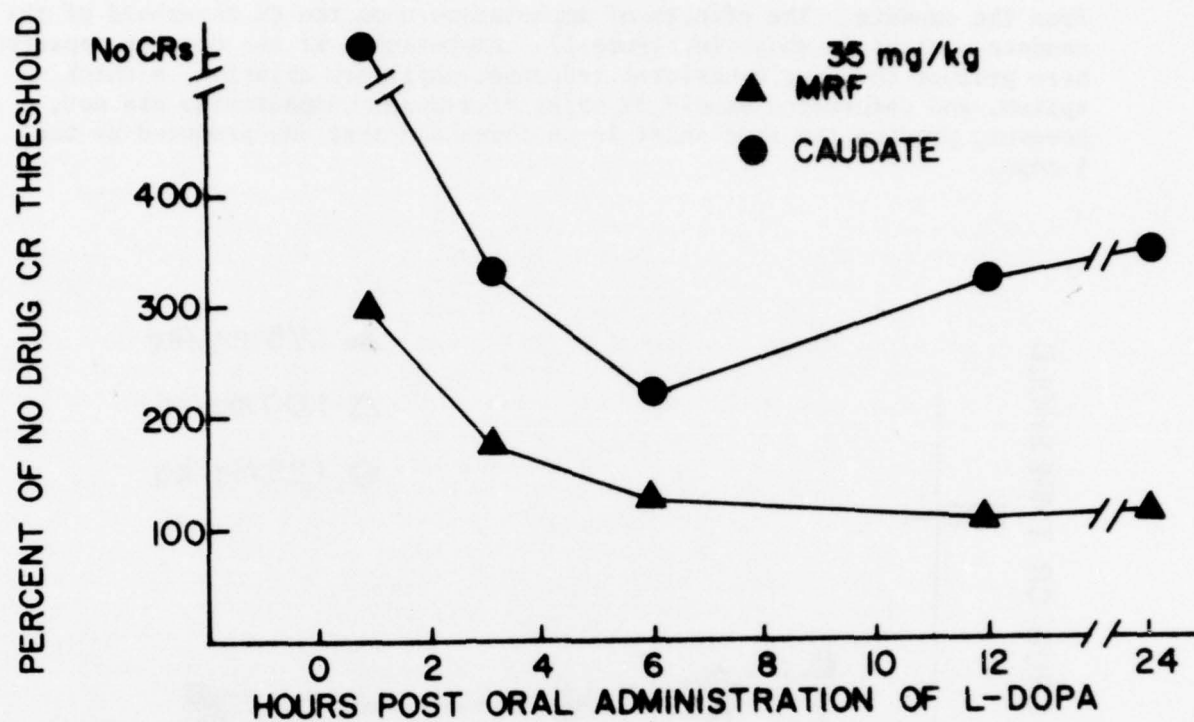


Figure 16. The effect of 35 mg/kg of l-dopa upon the conditioning threshold of the caudate nucleus and the reticular formation of cats previously addicted to pentobarbital (solid lines) or normal cats that have not been addicted to pentobarbital (dashed lines).

from the caudate. The effects of amphetamine upon the CR threshold of the caudate nucleus is shown in Figure 17. Amphetamine at the dosages reported here produce the same behavioral response, pupillary dilation, a thick spittle, and defecation as did 35 mg/kg of l-dopa. Amphetamine did not, however, produce the same shift in CR threshold that was produced by the l-dopa.

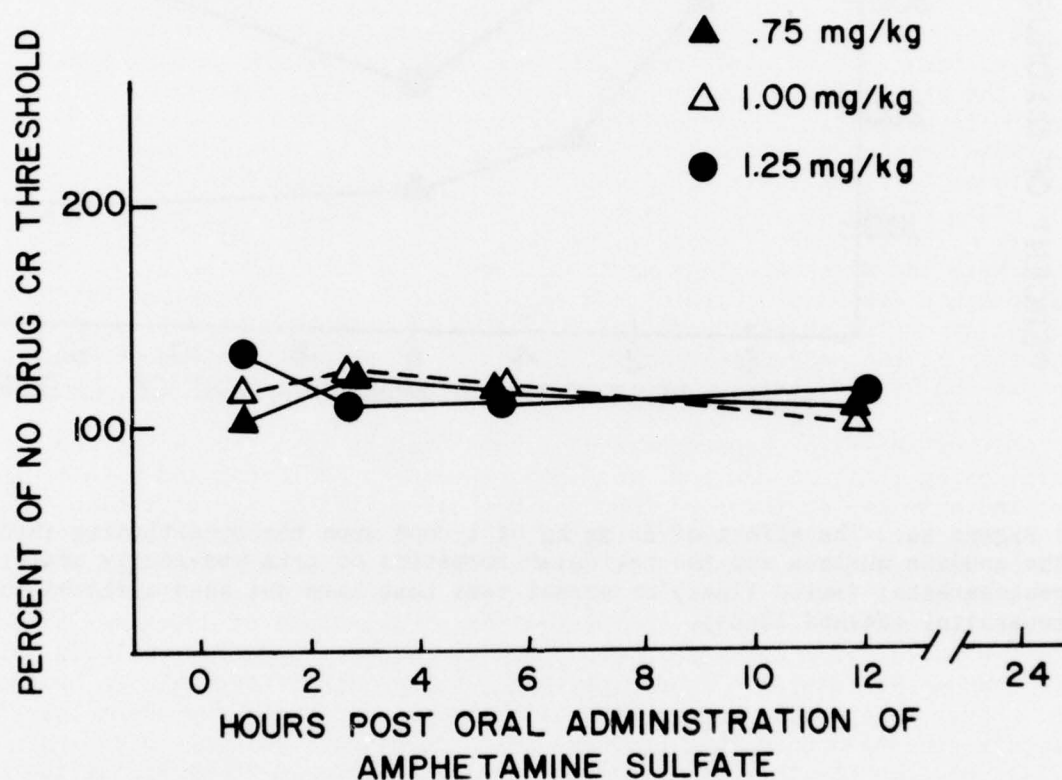


Figure 17. Effects of amphetamine sulfate on CR thresholds of the caudate nucleus.



The next experiment that we conducted to test the third hypothesis was to give cats undergoing withdrawal from pentobarbital a drug combination of 10 mg/kg librium and 50 mg/kg meprobamate. This combination was selected because it is long lasting; CRs were abolished in normal cats for eight hours and CR thresholds were still slightly above normal 24 hours later; the quality of the CRs was good; and this dosage level could substitute for a 15 mg/kg dose of pentobarbital and produce CR thresholds that were only slightly above those found for pentobarbital state dependent CRs. This drug combination failed to alter, in any way that we could identify, withdrawal symptoms and seizures.

At this point in the research, with no changes in brain excitability levels associated with withdrawal seizures, and the failure to in any way change the withdrawal seizures with the drug combination that produced the longest elevation of CR thresholds, (librium 10 mg/kg and meprobamate 50 mg/kg) we decided to change tactics. We decided to addict rats to phenobarbital and attempt to block their withdrawal seizures with the doses of drugs used on the cats. This was done to save the cats from repeated seizures, and we had only a few of them. Secondly, we believe on the basis of the data presented here and elsewhere that we could equate the doses of the drugs that produce state dependent learning and addiction. Finally, by selecting phenobarbital we could use pentobarbital to attempt to block withdrawal symptoms since this is the drug of choice for treatment of phenobarbital dependence (Goodman and Gilman, 1970).

Another series of experiments were conducted to test the third hypothesis, using rats. Because of the long process in addicting and withdrawing cats, and only two or three of them can be worked with at any give time, we decided to change animals and tactics so that a larger number of seizures could be screened at a time. Rats were addicted to phenobarbital and any changes in the latency of onset, duration, or other characteristics of the withdrawal symptoms following administration of a variety of drugs was noted. While the switch from cats to rats appears to present a species variable which could change the results of the experiment, we do not believe this to be the case. First, the dose of pentobarbital that produces state dependent learning in cats is the same dose that produces state dependent learning in the rat (12.5-15.0 mg/kg for the cat, reported here, and above 10-20 mg/kg for the rat (Overton, 1971). Thus, dosage level of pentobarbital that produces state dependent learning appears to be the same. Furthermore, for the rat, 80 mg/kg of phenobarbital is equivalent to 20 mg/kg pentobarbital or 200 mg/kg meprobamate (Barry, 1974), and 10 mg/kg pentobarbital should be equal to 100 mg/kg meprobamate, and they are the doses that we have found that just maintain state dependent learning in the cat. Thus, we felt that the drug dosage levels are sufficiently similar in the rat and cat that the species difference would not be a factor.

#### Experiment VI: Effects of Drugs on the Withdrawal Seizures of Rats

Method and procedure. Adult Wistar male rats were addicted to phenobarbital by adding the drug to dry-powdered rat chow in a concentration of 4.0 mg/kg of diet. All the animals were fed the diet for seven days and showed signs of intoxication which included staggering, falling on their sides, and occasionally, the loss of placing and righting responses.

The first symptom of withdrawal was trembling, which appeared in 24 hours, and an increased susceptibility to audiogenic seizures, which persisted in some animals for as long as 120 hours. No weight loss accompanied the addiction process, but there were marked reductions in both food intake and body weight during withdrawal. Attempts to block withdrawal symptoms, or delay their appearance, were made with a variety of drugs and drug combinations given 24 hours after the withdrawal of the drug, when the body trembling was beginning. Seizures were elicited by 30 seconds of white noise.

Table III shows the number of animals in each group and the proportion of animals from each group that had either severe running attacks or full tonic-clonic seizures when stimulated with white noise at various times after being withdrawn from phenobarbital. The drugs administered to block, retard, or alleviate the withdrawal symptoms, and the dosage levels are listed, not necessarily in the order in which they were tested. Neither librium, meprobamate, chloral hydrate, nor pentobarbital alone had any identifiable effects upon the withdrawal symptoms. When the drugs were tested in combinations, chloral hydrate was combined with meprobamate and with librium, and the librium and meprobamate were also combined with each other.

This gave us combinations that were long lasting (report number eight) and ones that would be expected to increase the thresholds of the caudate nucleus when substituted for pentobarbital (librium and meprobamate) or decrease the thresholds (meprobamate and chloral hydrate) or leave them unchanged (librium and chloral hydrate). The results are shown in Table III. The combinations with chloral hydrate were the best. In fact, with the first combination of meprobamate (50 mg/kg) and chloral hydrate (50 mg/kg), number eight in Table II, there was only one rat that had a seizure, and that rat had a seizure on the third, fourth, and fifth days after withdrawal. To verify, what we thought was a significant finding, that the combination of meprobamate (50 mg/kg) and chloral hydrate (50 mg/kg) was significantly reducing withdrawal symptoms, and to quantify it, the experiment was repeated on 16 new rats at the same dosage level; another group of rats was run at half the dose, while a third group was run at twice the dose. The results are shown in Table III as entries nine, ten and eleven, and it was clear that these treatments were without effect.

Another experiment was also conducted to arrive at a test of hypothesis number three. This experiment was based upon several considerations. The first was that the only area of the brain that we sampled, from which we identified consistent and permanent changes in conditioning thresholds, was the caudate nucleus. The second consideration came from the fact that l-dopa produced different effects upon the conditioning thresholds of the caudate nucleus, depending upon whether the animals had been previously addicted or not. The third consideration stemmed from the fact that the caudate nucleus has the highest concentration of dopamine in the brain and, in report number eight, we suggested that the neurotransmitter most likely involved in the addictive process was dopamine. In addition, the recovery from addiction may involve restoring the caudate nucleus to its pre-addiction threshold. With these considerations, another series of experiments was conducted to determine whether l-dopa would block or retard withdrawal seizures. The rationale for this series was that l-dopa would return the caudate nucleus to its pre-addiction level of functioning for a given period of time, depending on the dose.

	Dose (mg/kg) & Rte. of Admin.	Proportion of Animals Having Seizures after Withdrawal of Pentobarbital at (hours)					Total n=168
		24	48	72	96	120	
1. Controls	0	.04	.67	.67	.46	.38	24
2. Librium	20 ip	.13	.38	.50	.25	.13	8
3. Meprobamate	100 oral	0	.75	.63	.38	.25	8
4. Chloral Hydrate	100 oral	.13	.25	.75	.63	.25	8
5. Pentobarbital	25 ip	.13	.38	.50	.38	.38	8
6. Librium + Meprobamate	10 ip/ 50 oral	0	.38	.38	.25	.25	8
7. Librium + Chloral Hydrate	10 ip/ 50 oral	0	.25	.25	.25	.25	8
8. Meprobamate + Chloral Hydrate	50 oral/ 50 oral	0	0	.13*	.13	.13	8
9. Meprobamate + Chloral Hydrate	50 oral/ 50 oral	.17	.58	.67	.50	.25	16
10. Meprobamate + Chloral Hydrate	25 oral/ 25 oral	0	.25	.75	.38	.13	8
11. Meprobamate + Chloral Hydrate	100 oral/ 100 oral	.25	.50	.50	.50	.25	8
12. L-Dopa	25 oral	.13	.63	.63	.50	.25	8
13. L-Dopa	50 oral	.08	.37*	.20*	.13*	.04	24
14. L-Dopa	100 oral	0	.12*	.25	.25	0	8
15. L-Dopa	150 oral	0	.37	.37	.13	.13	8
16. L-Dopa + Meprobamate + Chloral Hydrate	25 oral/ 50 oral/ 50 oral	0	.25	.25	.25	.13	8

\*Significantly different from controls at the .05 level or greater.

Table III. The proportion of animals showing either severe running fits or convulsions upon stimulation with white noise, and given a drug to block withdrawal seizures. Statistical test was for the z test for the significance of difference between proportions.



Rats were given phenobarbital in their food for seven days to addict them and then the pentobarbital was withheld and attempts were made to block the withdrawal seizures and running fits with the administration of various doses of l-dopa, or 25 mg/kg l-dopa combined with 50 mg/kg meprobamate and 50 mg/kg chloral hydrate, 24 hours after phenobarbital was withdrawn. In the initial experiment there were eight animals in each group. The experiment was repeated with an additional 16 animals receiving 50 mg/kg l-dopa. The results are summarized in Table III, entries 12, 13, 14, 15, and 16. The results showed that the rats given 50 mg/kg l-dopa had a significantly lower incidence of withdrawal symptoms and seizures than did the controls. In addition, the rats that received 100 mg/kg chloral hydrate had significantly fewer seizures 48 and 72 hours after withdrawal than did the controls.

To verify the finding that l-dopa significantly altered the proportion of phenobarbital dependent rats showing withdrawal symptoms when phenobarbital was removed from the animals' food, another experiment was conducted again using various dosage levels of l-dopa to block the withdrawal symptoms. The food of 80 rats was adulterated with phenobarbital for seven days, when it was removed. The number of sound elicited convulsions and running fits were recorded and the effects of orally administered l-dopa, and in the quantities of 50, 100, and 150 mg/kg, upon the withdrawal symptoms, was followed. The results are shown in Table IV. The proportion of rats showing withdrawal symptoms was not different from the controls with any dosage level of l-dopa used. No drug or drug combination, that we have tried, has consistently blocked or altered the incidence of withdrawal seizures in rats dependent upon phenobarbital.

		Proportion of Animals Having Seizures After Withdrawal of Pentobarbital at (hours)					
	Oral dose mg/kg	24	48	72	96	120	N
Controls	0	0	.40	.60	.45	.25	20
l-dopa	50	0	.35	.45	.40	.25	20
l-dopa	100	0	.45	.45	.35	.15	20
l-dopa	150	0	.40	.60	.35	.10	20

Table IV. Proportion of animals showing withdrawal seizures after oral administration of l-dopa.

Some comments about the data reported in Tables II and III should be made. First, the data was analyzed by using the  $z$  test for the significance of the difference between proportions (Guilford, 1965; pp. 186-187). The cases where there was a significant difference between the proportion of



rats in the control and experimental groups that had withdrawal seizures is indicated by an asterisk. The only groups that showed significantly fewer seizures than the control group were the rats in Group 8, that received 50 mg/kg meprobamate and 50 mg/kg chloral hydrate, and Group 13 and 14 that received 50 mg/kg or 100 mg/kg l-dopa. No other differences were found to be statistically reliable. The failure of some of the other differences to be reliable, e.g., groups 4, 7, and 10, was a function of the size of N. With Np for the various groups smaller than 10, a corrections for continuity was required and these differences failed to reach significance. However, I feel that none of the groups are reliably different from the controls. In those instances where the differences between the experimentals and controls exceeded the .05 level of confidence the experiment was repeated with naive animals to replicate the findings. In no instance, when the experiment was repeated were the findings replicated. Thus, the drugs used in these experiments to block withdrawal seizures were ineffective in doing so. It is clear from this data that the third and fourth hypotheses were not confirmed, and no drug combination we have tested has in any way significantly altered the course of the withdrawal symptoms.

Experiment VII: A Comparison of Drug Effects Upon Conditioned Responses Established to Peripheral Stimulation or to Direct Electrical Stimulation of the Brain

One of the characteristics of drugs that produce state dependent learning is that their effects are on the central nervous system. Drugs that act peripherally do not produce state dependent learning while those that act centrally do (Black, Carlson, and Solomon, 1962; Kumar, Stolerman, and Stienberg, 1970; Overton, 1968). Despite the fact that state dependent learning cannot be produced by drugs that have only peripheral effects, one of the theories of state dependent learning is the drug-stimulus hypothesis advanced by Brown, Feldman, and Moore, 1962, and Otis, 1964. This hypothesis is that the presence of a drug produces a physiological state which has stimulus characteristics which are on a continuum with the normal state. The stimulus characteristics of the drugged state act as a discriminative stimulus and exert control over the response. Bliss (1974) has reviewed the drug-stimulus hypothesis and presented evidence and arguments against. Furthermore, Chute and Wright (1973) show that post-trial administration of pentobarbital produces state dependent learning. The CR was present after post learning trial injection of pentobarbital and a pre-retention trial injection, thereby eliminating drug-stimulus characteristics that would have been present during learning. In addition, Pusakulich and Nielson (1976) have specifically investigated the kinds of cues that pentobarbital drugged and non-drugged animals used to learn a water maze. They found that drugged animals use different cues in the different state, and that rats could not learn to use different cues when the drugged state was held constant across tasks. They concluded that the drugged state and the normal state were not on the same continuum since the drugged state impairs the capacity of the drugged animals to use environmental stimuli.

This experiment was conducted to compare the effect of pentobarbital upon CRs established to peripheral stimulation, i.e., to a tone CS, and to a CS applied directly to the brain. We wanted to know whether drugs, in this case pentobarbital, differentially influence central or peripheral

neural processes. If, in the same animal, CRs established to a peripheral stimulus such as tone, are abolished at one dose level but CRs established to central stimulation are still intact, at that dose level, then certainly the differential responding is not mediated by any drug-stimulus conditions since the drug stimulus conditions are surely the same for the two responses since it is the same animal.

The same general procedure was used in this experiment as in the first experiment. However, one difference was that these cats were trained to give CRs to a 1000 Hz tone in addition to having CRs established to electrical stimulation of a subcortical brain area, either the medial geniculate body, hippocampus, or caudate nucleus and thresholds were determined. In addition, we attempted to train four cats to the tone CS and two cats to a light CS while they were drugged with 13.5 mg/kg pentobarbital as in experiment II. Despite the fact that we gave the cats that were trained to either the tone or light CR up to ten times the number of training trials, that the animals that were trained to the tone CS in the normal state received, we could not establish CRs to either a tone or a light CS in any animal so we discontinued training them. The eight cats that were trained in the normal state to respond to either the tone or the central CS were then given different doses of pentobarbital and the effects upon both the tone elicited and the centrally elicited CRs were determined. In addition, the intensity of the tone CS was varied from 60 to 105 decibels, measured at the cat's ear, to determine whether the intensity of the tone CS was a factor in maintaining the CR when the cats were in a drugged state.

The first finding was that cats could not, apparently be trained to give CRs to either a tone or light CS. The average number of trials to criterion to tone for the nondrugged trained animals was 290, and the average number of trials reported by Doty et al. (1956) was 281 for tone CS and 289 for light CS. We gave over 5000 trials to the light CS, and over 3000 trials to the tone CS before we concluded that they could not give CRs to these peripheral CSs.

The second finding was that the normally trained cats, when given a dose of pentobarbital stopped responding to the tone CS at doses of pentobarbital that left the centrally elicited CRs intact. These results are summarized in Figure 18. Without exception the CRs established to the tone CS were abolished at a lower drug dosage than were the CRs elicited by central stimulation. Figure 18 compares the very rapid drop off in CRs established to the tone CR while the CRs established to central stimulation are still intact and show only a relatively small increase in threshold. The CRs established to the tone CS are abolished at much lower dosages than are those established to central stimulation. It is pointed out in Figure 19 that the failure to respond to the tone cannot be due to any motor impairment since the same animals were still responding to the central stimulation with only slight increases in thresholds. Another finding that is apparent is that the drug-stimulus hypothesis is no longer tenable as the basis for state dependent learning because there is differential responding to the peripheral and central CSs with no changes in the drug-stimulus complex. These cats simply did not respond to the tone CS but did to the central CS. This differential responding to the peripheral and centrally elicited CRs, while

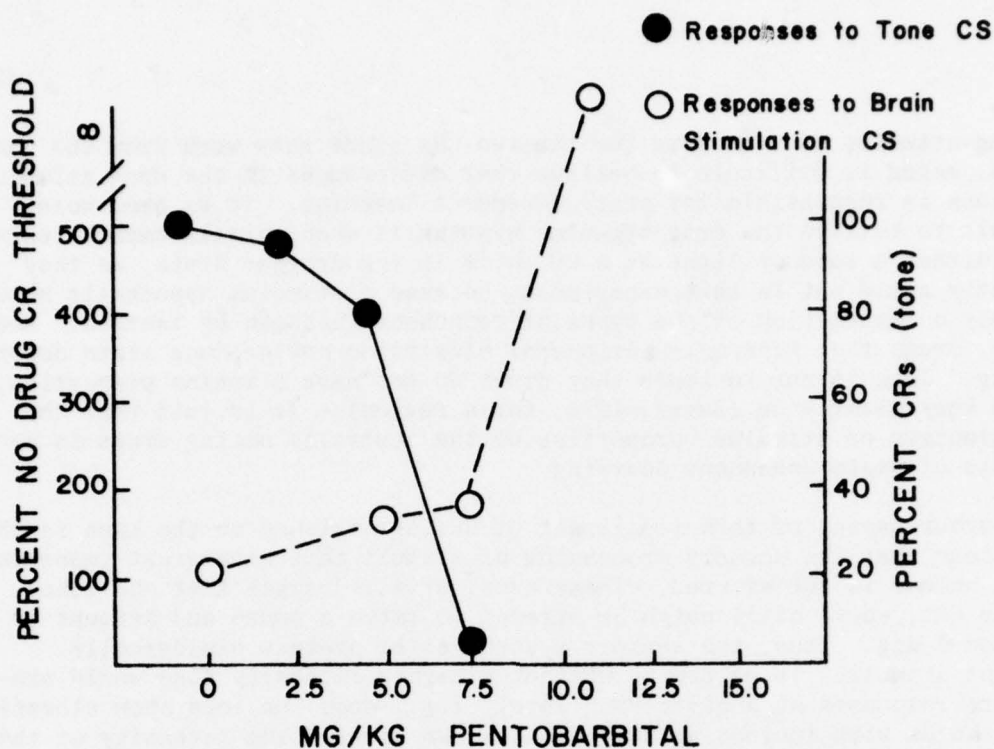


Figure 18. Comparison of the effects of Pentobarbital upon the conditioned responses established in the normal state to a tone or to brain stimulation as the CS.

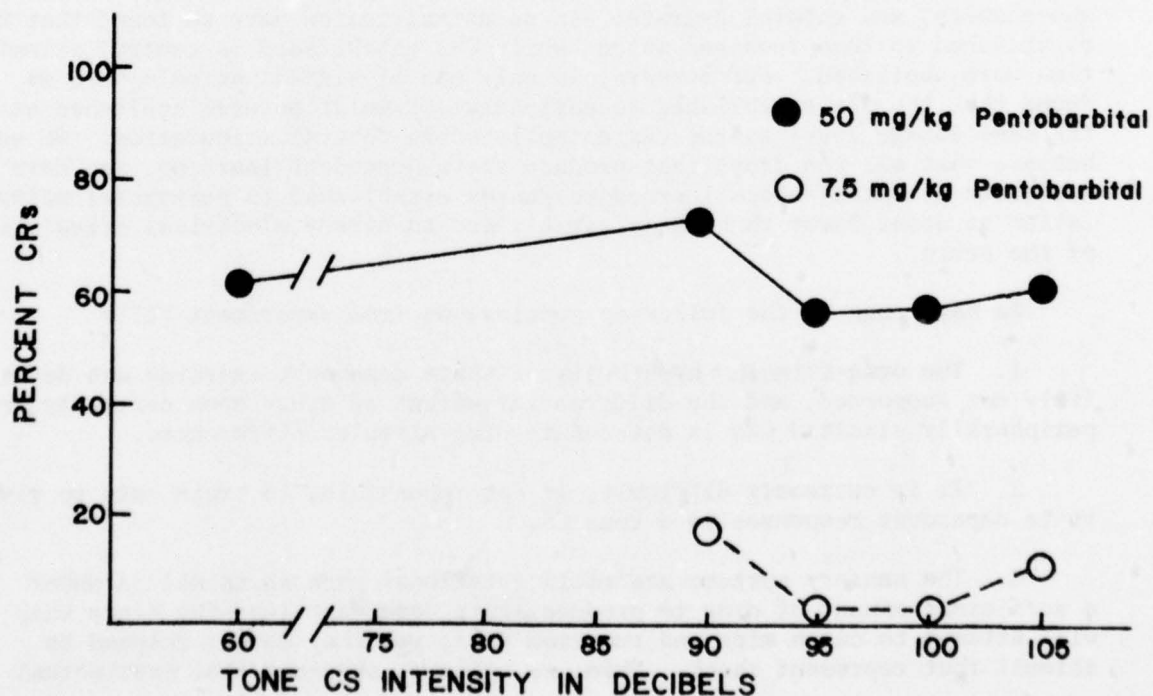


Figure 19. Percent CRs as a function of the intensity of the tone CS. The intensity of the CS was measured as the cats ears.



the drug-stimulus was the same for the two CRs since they were from the same animals, makes it difficult to believe that differences in the drug stimulus conditions is responsible for state dependent learning. It is even more difficult to believe the drug-stimulus hypothesis when animals cannot learn to use either a tone or light as a CS while in the drugged state, as they apparently could not in this experiment, because a stimulus hypothesis should not imply a restriction of the types of responses that can be learned. And finally, drugs that have only peripheral effects do not produce state dependent learning. This is not to imply that drugs do not have stimulus properties, because they clearly do (Barry, 1974, for a review). It is just that the discriminative or stimulus properties of the centrally acting drugs is not the basis of state dependent learning.

Another aspect of this impairment of CRs established to the tone is that it is clear that the sensory processing of stimuli that have great importance for the animal is not altered. These cats, at all dosages that abolished the tone CRs, would still catch or attempt to catch a mouse and attempt to flee from a dog. Thus, the sensory systems still process biologically important stimuli. To determine whether a higher intensity tone would produce more responses at a given drug level, i.e., does the tone show elevation in thresholds with increasing drug dosages, we plotted the intensity of the tone in decibels measured at the cat's ear, against the percentage of CRs. This is shown in Figure 19. There was no relationship between the intensity of the tone CS and the number of CRs that were elicited. There was no evidence that the sensory systems had changed threshold.

The finding reported above, that pentobarbital abolishes CRs established to peripheral stimulation while leaving CRs established to direct electrical stimulation of the brain intact has since been expanded to include librium, meprobamate, and chloral hydrate. In no animal tested have we found that CRs established to tone remained intact while CRs established to central stimulation were abolished. Furthermore, in only one of sixteen animals have we found that the CRs established to peripheral stimulation were abolished at the same dosage level as the CRs established to central stimulation. We now believe that all the drugs that produce state dependent learning, and have addiction potential block learned responses established to peripheral stimulation at doses lower than those established to direct electrical stimulation of the brain.

We have come to the following conclusions from experiment VIII:

1. The drug-stimulus hypothesis of state dependent learning was definitely not supported, and the differential effect of drugs upon centrally or peripherally elicited CRs is not due to drug-stimulus differences.
2. It is extremely difficult, if not impossible, to train cats to give state dependent responses to a tone CS.
3. The sensory systems are still functional when an animal is under a sufficient amount of drug to produce state dependent learning since they will attempt to catch mice and run from dogs, yet they do not respond to stimuli that represent shock. This, we believe, suggests that instinctual



type behavior can still be guided by sensory stimulation, but softer type of behavior that is heavily dependent upon learning is disrupted by drug dosages necessary to produce state dependent learning, and furthermore, new learning requiring sensory guidance cannot occur.

With the addition of the results presented here, there is a considerable amount of evidence that pentobarbital and other pharmacologically related drugs differentially affect the utilization of peripheral and central stimulation. Pusakulich and Nielson (1976) found that it was virtually impossible to train drugged rats to utilize distal cues in the solution of a water maze escape problem. The same animals, however, acquired response solutions with relatively little difficulty. Bliss (1974) found similar effects of pentobarbital on discrimination responses in monkeys. Visual discriminations proved to be more affected by the drug than did response (pressing a left versus pressing a right door) discriminations. Results of two earlier studies by Weiskrantz (Weiskrantz and Baltzer, 1965; Gross and Weiskrantz, 1961) are consistent with the results of both of these studies and with the results presented here but indicate that there may not be a clear distinction between drug effects on central and peripheral stimuli. Those experimenters gave monkeys training in a visual or an auditory discrimination task and in a delayed response task and then tested for retention of responding while the animals were drugged with meprobamate. Of the three tasks, the drug disrupted performance of the auditory task the most severely. Performance on the visual discrimination task was also disrupted by the drug but performance on the delayed response task was the same or better than normal. Apparently related to these same effects, Weiskrantz has also noted that meprobamate ameliorates difficulties that monkeys with frontal cortex lesions have in the solution of delayed response problems. The animals are typically described as being highly distractible and meprobamate presumably modulates the ability of the animals to attend to or otherwise utilize background stimuli.

The exact nature of the changes which might underly drug produced sensory restriction is of course uncertain. It seems unlikely, however, that they are simple reception deficits. Drugged animals behave quite appropriately in a variety of situations and may exhibit behaviors which presumably require the processing of a great deal of sensory stimuli. It is a common observation, for instance, that if food is available, that animals drugged with pentobarbital will eat until they are nearly unconscious. Similarly, though they are quite clumsy, drugged animals will attempt to elude capture if placed in an open area. Drugged cats and drugged rats with histories of killing mice while nondrugged will pursue and kill mice while under doses of barbiturates which completely disrupt conditioned responses. This was most impressively demonstrated with one of the cats in the experiment described above. The particular animal did not respond to tone or to brain stimulation while under even the smallest test dose of pentobarbital (5 mg/kg) but pursued and killed a mouse while under 7.5 mg/kg. Under 10.0 mg/kg, the animal was ineffectual in its attempts but nevertheless, pursued a mouse for the three minutes duration of the test. It is of course a truism that an animal cannot be conditioned to respond to a stimulus or configuration of stimuli unless the animal can sense the stimulation. There are reports of successful drug conditioning with visual, auditory and position conditioned stimuli. It seems, therefore, that the drugged animal is at once both sensitive and

insensitive to sensory stimulation. An explanation for the apparent paradoxical situation is that depressants interfere with cross modality sensory integration. Pusakulich and Nielson, for instance, have noted that maze learning in normal rats involves at the very least, the integration of visual and body position cues. Their findings were that drugged animals cannot learn to utilize distal cues but can learn a sequence of responses to escape a water maze. Learning under a drug may thus be both simpler and more restricted than that in the normal state. This is, in fact perfectly consistent with observations that drugged rats learn some simple approach or avoidance responses more readily than do normal animals but have great difficulty with discrimination tasks and responses requiring delayed responses (Sachs, 1967).

We have tentatively concluded, from our results on the brain threshold shifts produced by addiction, and the differential effect upon the auditory system to date, that the addictive process is characterized by a double dissociation. Initially it is characterized by a dissociation of the peripheral from the central nervous system, and the central nervous system becomes "free running" and is no longer under stimulus control. As drugged conditions continue, there is a further dissociation, between the arousal system and the motor system. This is reflected in the shifts in CR thresholds of the caudate nucleus but not the reticular formation and, this dissociation appears to be permanent.

#### Discussion and Conclusions

I wish to comment about the range of stimulus intensities that we use in these experiments. When a cat has been implanted and before it is trained to give CRs to electrical stimulation of the brain, it is stimulated at all electrode placements with a wide range of stimulus intensities. This preliminary screening of the animal is so that we will know what kinds of movements and at what intensities movements are elicited. This is a routine screening of animals so that we do not select a conditioning site which gives us any forced movement that could interfere with the cats learning the flexion CR, that could masquerade as a conditioned response, or that is obtained with low intensity stimulation. We do try to find forced movements that won't interfere with the cats learning and that are obtained with moderate (.9 to 1.2 milliamperes) stimulation. We then follow the effects of the drugs and drug treatments upon these forced movement thresholds. In fact, Girden and Culler, when they first described "dissociation of learning" measured elevation as forced movement thresholds and described the dissociation of learning as a functional decortication. The reason we do not routinely describe in our method section how we obtain forced movement thresholds, and the fact that we follow them is because we cannot always count on obtaining them. It is something we follow when we can.

The thresholds for seizures were determined and we have filmed the entire seizure sequence with the seizure elicited by several different stimulus intensities. The topography of the seizures are reliable and the same to different intensities. The duration of the components is related to the intensity of the eliciting stimulus. However, as the cats have been receiving the addicting drug sequence, their seizure thresholds have increased. The topography of the seizures when they are in a drugged condition is not related

to the stimulus intensity but rather to the current that the stimulating intensity is above the threshold. This is true for the CR thresholds also. Intensities of CS stimulation that the animal would not and could not tolerate in the normal state are frequently below threshold when the animal is drugged. Thus we use a wide range of stimulus intensities, it is just that often the threshold has been elevated and the cat does not respond. Thus the stimulus intensity is related to the animal's drugged state, or threshold, and has meaning only in that context.

Furthermore, when we initially train an animal we always try to use a stimulus intensity that we are reasonably sure the animal can perceive, i.e., one that is well above threshold. We have no desire to spend time training a cat with a stimulus that the cat might not be able to respond to. Consequently, we select a fairly high CS intensity. A scan of the training protocols show that the intensity of our training stimuli range from 2 to 4 times their threshold. We have no way of knowing before the animal is conditioned where we are in relationship to the threshold. The cat can only tell us whether he can detect the stimulus or not by making a conditioned response.

There is one final point and that is the range of CR thresholds in the normal state. The range of the CR thresholds for the mesencephalic reticular formation is from .03 to .5 milliamperes with a mode of .05 milliamperes; the caudate nucleus from .2 to .7 milliamperes with a mode of .5 milliamperes; and the medial geniculate body from .1 to .2 milliamperes with a mode of .14 milliamperes. In the drugged state the thresholds for the mesencephalic reticular formation may reach .35 mA before the CRs are lost, while those of the caudate have reached 3.5 milliamperes and the medial geniculate thresholds have reached 1.45 before the CRs are lost. This brings us to another point about our range of CR intensities. When a cat has been drugged with a dose of pentobarbital that abolishes CRs, we use stimulating intensities up to 10 times those found in the normal state and frequently five times the CS intensities that last produced CRs. Thus we commonly use a range of CR intensities that range from normal state CR threshold intensities up to 10 times the threshold intensities.

To compare the drug effects we have obtained with different thresholds, even within the same structure, we have made the comparison on the basis of percentage CR threshold change. We could have graphed the results in terms of threshold intensity (milliamperes) and shown that there were threshold differences across structures. This information is available, however, and we chose to present the data in terms of relative effect, or percentages, because the drugs do seem to have the same relative effect. This we believed to be more important than to restate the findings that areas of the brain vary in sensitivity. I have taken the liberty of enclosing Figure 20, which is previous work which shows the CR thresholds of various brain areas as a function of frequency of the CS.

The conditioning procedure used here is responsive to drug administration both in terms of the time course of action of a drug, and to different doses of the same drug. Furthermore, the different drugs and drug doses could be equilibrated in terms of their effects in normal animals on the basis of



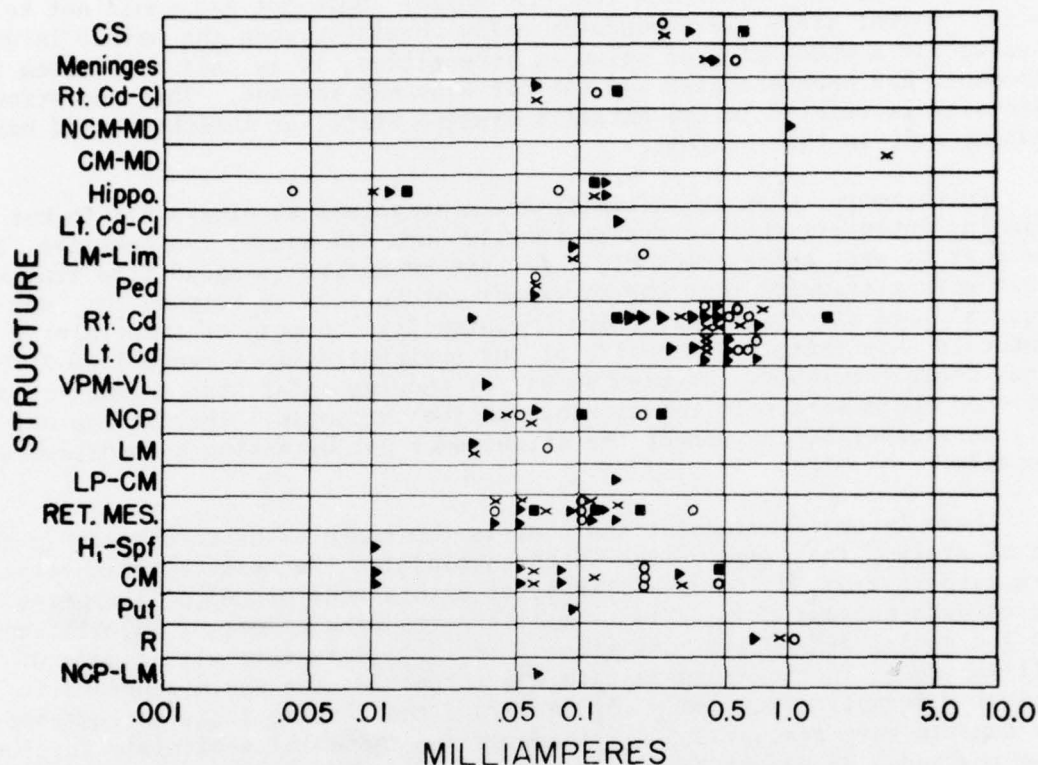


Figure 16. (Nielson, et al., 1962) Thresholds of electrical stimulation provoking avoidance conditioned responses. (Symbols indicate stimulus frequencies in pulses per second: Triangles, 300 p/s; crosses, 150 p/s; circles, 30 p/s; squares, 3 p/s). Note-- VA, N. ventralis anterior; R+Cd, N. caudatus, right head; RET MES, substantia reticularis mesencephalica; Mm, Corpus mam-millare; R, N. reticularis; LM, lemniscus medialis; L+Cd, N. caudatus, left head; Lim, N. limitans; CM, N. centrum medianum; Put, Putamen; H<sub>1</sub>-Spf, Forel's field H<sub>1</sub> and N. sub-parafascicularis; VPM-VL, N. ventralis posteromedialis and N. ventralis lateralis; CI, capsula interna; NCM-MD, N. cen-tralis medialis and N. medialis dorsalis; NCP, N. commissurae posterioris; LP, N. lateralis posterior; Ped, pedunculus cere-bralis; CS, colliculus superior; Hippo, hippocampus.



their brain threshold shifts. They were also equated for their psychological or cognitive effect in terms of their ability to maintain state dependent learning in those animals whose only CRs were state dependent. These CR thresholds as a measure of perception are lower than thresholds required to produce motivational effects (Nielson, Doty, and Rutledge, 1958). In addition, these thresholds are stable for as long as two years (Nielson and Davis, 1966), are sensitive, to the effects of electroconvulsive shock (Nielson, 1968), to brain lesions remote from the site of stimulation (Nielson and Davis, 1966), shows stimulus strength-duration relationships; and for further discussion of this method and additional controls the reader is referred to Doty, Rutledge and Larsen (1956) where microphotographs of the neural tissue surrounding cortical electrodes is available for inspection, and where they used CS intensities two to three times those used here.

This research was undertaken in an attempt to find a drug, or a combination of drugs that would block seizures that followed the withdrawal to pentobarbital. The end point of the research was to block a behavior--a seizure--the end point of this research must, therefore, be behavioral. Furthermore, that response to withdrawal from drugs can be, and frequently is, a form of a conditioned response is well known and has been discussed extensively (e.g., Vaillant, 1969). Thus, the fact of a withdrawal seizure is a behavioral response. The dispute is on the nature of the mechanism that mediates that withdrawal response. The hypotheses that have been advanced to explain the mechanism that mediates withdrawal have been, learning in some cases, supersensitivity in others, and shifts in brain excitability levels in others. This research was undertaken with the belief that, in these experiments learning would not be a factor in withdrawal symptoms, but rather, withdrawal seizures reflected a change in the excitability of the central nervous system. This is an assumption that is generally accepted in the literature as true and usually without citing a source. I believe that one of the outcomes of this research should be to abandon the notion of a change in excitability level of the central nervous system as an explanatory construct of how behavioral seizures are mediated. First of all, I will summarize why I believe the conditioning method used here is at least as good as other methods used to infer the existence of an hyper- or hypo-excitability nervous system. The characteristics of this method are that the behavior has an identifiable threshold which:

1. can be quantified for stimulus intensity;
2. for which a strength-duration curve of the stimulus parameters can be generated;
3. it is sensitive to different doses of a drug;
4. it is sensitive to the duration of action of different doses of a drug;
5. strength-duration curves for a variety of drugs can be generated;
6. is not due to stimulation of the meninges or blood vessels because the threshold for CRs elicited by stimulation of CNS structures is lower than for stimulation of meninges or blood vessels (see Doty et al., 1956);
7. the thresholds are sensitive, in non-drugged trained animals to a variety of agents such as drugs, electroconvulsive shock, and brain lesions, that are thought to reflect changes in the excitability of the central nervous system; and
8. the CR threshold (detection or perceptual) is below the threshold for producing motivational changes.

The findings of this experiment have led me to question the assumption upon which this research was based. Namely, that withdrawal seizures and symptoms represent a hyperexcitable nervous system, and another assumption, that drugs that depress that hyperexcitability will alleviate those symptoms.

The hyperexcitability of the nervous system is, without being exhaustive, inferred from behaviors such as the withdrawal symptoms themselves, or inferred from other behaviors such as changes in open field or exploratory behavior (Goudie and Taylor, 1973), inferred from somatosensory evoked potentials (Shagass, 1972), auditory evoked potentials (Jarvilehto, Laakso, and Virsu, 1975), EEG changes (Killam and Killam, 1957; Bradley, 1957), EEG changes after an injection of drug antagonists (Sharpless and Jaffe, 1966, 1969) susceptibility to audiogenic seizures (Freud and Walker, 1971), susceptibility to seizures in mice following lifting (Goldstein, 1972), or changes in threshold of electroconvulsive shock (McQuarrie and Fingl, 1958), to list a few of the experimental operations used to infer changes in the excitability levels of the central nervous system. Thus excitability of the central nervous system is usually inferred, either from behavior, or from electrical activity recorded from the central nervous system.

We are going to argue here, that one of the assumptions upon which this research was based, an assumption which is generally accepted in literature as true without usually citing a source, that the withdrawal syndrome is characterized by a hyperexcitable nervous system, is false, and obstructing a solution to the problem of management of withdrawal symptoms.

The first step in this argument is to question whether electrical responses recorded from the central nervous system do in fact measure brain excitability. First of all, we do not now have a clear definition of "excitability." Apparently the term "brain excitability" is used in an analogous fashion to the excitability of the neuron, and excitability cycle of the neuron described only in terms of its threshold (Morgan, 1965). The various phases in the excitability cycle of the neuron, the period of latent addition, relative refractory period, supernormal or subnormal periods, all have meaning only in terms of the threshold of that neuron. The first requirement of a statement about excitability, whether of the single neuron or of the whole brain should be in terms of threshold. None of the other measures of hyperexcitability of the central nervous system are based upon thresholds.

The procedures that use evoked potentials to identify changes in brain excitability levels (e.g., Jarvilehto et al., 1975; Begleiter et al., 1974) use changes in amplitude of the evoked response as their measure, with an increase in amplitude taken as evidence of hyperexcitability. Drugging an animal will increase the amplitude of the evoked potential, and this is with a single dose that is known to depress the central nervous system. Pentobarbital in the dose of 10 mg/kg in the cat has been shown to block the inhibitory effect of reticular stimulation upon the auditory evoked response. Thus pentobarbital in a dose of 10 mg/kg is thought to inhibit the normal inhibition that the reticular formation shows on auditory evoked potentials and they increase in size (Killam and Killam, 1958). However, the direction of change of amplitude of the evoked response need not be consistent for investigators to infer changes in excitability levels. Alcohol, which is

cross tolerant with pentobarbital has an opposite effect on the auditory evoked response, i.e., decreases its amplitude (Gross, Begleiter, Tobin, and Kissen, 1966). Jarvilehto et al. (1975) recorded auditory evoked responses, and also took audiograms so that they had a measure of peripheral sensitivity that paralleled their evoked response. They found that the amplitude of the evoked response during hangover in humans was like that found in the intoxicated state, and that auditory thresholds as measured by the audiogram did not change while the evoked responses did. They concluded that during hangover the central nervous system is not in a state of hyperexcitability. Furthermore, they point out that there is a dissociation between the peripheral threshold and the electrical response (evoked response) which is supposed to be a measure of auditory sensitivity (Bruian, 1969). This dissociation of electrical events recorded from the central nervous system and behavioral events will be encountered again.

The EEG changes that have been taken as evidence of changes in brain excitability levels involve the recording of epileptiform-like activity, or slow waves indicative of the drugged state, and then inferring the state of the nervous system. This procedure, like the recording of evoked potentials, has no threshold functions to relate excitability to. It is just as perilous, however, because there is frequently a dissociation of EEG activity and behavior. Bradley (1958) has pointed out the importance of measuring both the behavior and the EEG activity because of this dissociation between behavior and EEG patterns. His data showed that cats were behaviorally active while under the influence of atrophine but had EEG patterns characteristic of sleep. The dissociation of EEG activity and behavior is also seen during self-stimulation. The self-stimulation, first described by Olds and Milner in 1954, is a phenomenon in which animals that are given the opportunity to press a bar, and thereby electrically stimulate certain areas of their brain, press the bar at high rates for long periods of time, frequently to the exclusion of other reinforcers. Nielson, Doty and Rutledge (1958) compared the threshold for self-stimulation with the thresholds for perception (the conditioning thresholds reported here) and found that the conditioning thresholds were always lower than those for self-stimulation. They also reported that cats that were self-stimulating appeared to be having seizures. Subsequently, Porter et al. (1959) reported that EEG recordings showed that self-stimulation was accompanied by epileptiform activity. Bogacz and Olds (1965) subsequently investigated the relationship between seizure-like activity and the thresholds for self-stimulation, and whether the seizures were part of the incentive for self-stimulation. They found that self-stimulation was accompanied by EEG recordings characteristic of epileptiform activity at some sites but not at others; that from those sites which produced both epileptiform activity and self-stimulation, that the threshold for self-stimulation was initially always lower than the threshold for epileptiform activity. With time, some of the thresholds for epileptiform activity, but not all, and in some areas, but not all, became lower than the thresholds for self-stimulation. They concluded that epileptiform activity was not necessary for self-stimulation, and had nothing to do with it, even though epileptiform activity always accompanied self-stimulation at certain intensities at certain brain sites. The thresholds for self-stimulation remained stable despite the presence or absence of EEG seizure-like activity, which in turn did not change the self-stimulation thresholds. Similarly, Nielson, Justensen, and Porter (1968) produced hippocampal seizures and recorded that seizure activity as it spread throughout the brain. Immediately



after recording the seizure activity they determined whether the seizure activity had produced any change in conditioning thresholds. They subsequently produced hippocampal seizure activity while the cats were under the influence of various anticonvulsant drugs, again followed the routing of the seizure activity through the brain and again determined conditioning thresholds. The various anticonvulsant drugs tested, Tridione, mysoline, phenurone, phenobarbital, and dilantin produced distinctively different patterns of hippocampal seizure activity both in terms of the different brain areas showing the activity and the EEG pattern, but the presence or absence of seizure activity in a particular structure was totally unrelated to whether the drug changed the conditioning threshold of that structure. Thus EEG recordings of seizure activity are unrelated to conditioning thresholds, or to thresholds for self-stimulation. It seems reasonable to conclude that the presence or absence of the electrical signs of seizure activity are unrelated to brain excitability changes as measured by two different behavioral measures based upon thresholds obtained by direct electrical stimulation of the brain.

The behavioral measures from which hyperexcitability of the central nervous system is inferred, hyperactivity, increased in open field and exploratory behavior (e.g., Goudie and Taylor, 1973) produce some interesting problems. Lesions or ablations of the central nervous system may also produce these same behavioral effects, but we have yet to see them described as being due to hyper-excitability of the central nervous system. It is well known that increases in activity, and open field, and exploratory behavior are produced by frontal ablations (Zubek and de Lorenzo, 1952) but the deficit is not attributed to a hyperexcitable nervous system, but to loss of memory (Jacobsen, 1936), then to loss of inhibition (Konorski, 1961), or loss of response suppression (Rosvold and Mishkin, 1961), or disinhibition of inhibition (Gerbner and Pasztore, 1965). Increases in activity levels or exploratory behavior are never attributed to changes in excitability of the central nervous system when they follow experimental manipulations such as ablations, lesions, changes in feeding schedules, or infantile handling. There is no special reason to infer changes in brain excitability from these behavioral changes, simply because the animals were given a drug.

If there is one specific paper that is cited as evidence for a hyperexcitable nervous system following withdrawal of alcohol, it is the paper by McQuarrie and Fingl (1958). They reported a progressive decrease of the electroconvulsive shock (ECS) threshold following withdrawal from alcohol. When references are cited as evidence of central nervous hyperexcitability during drug withdrawal, this is the article most frequently cited. However, there are certain considerations that make it difficult to believe that this paper is a sufficient basis for inferring hyperexcitability of the central nervous system. The first is that their findings have not been confirmed (Ratcliff, 1972). The second is that ECS thresholds are lowered by restraint, (Seinyard, Radnakrishnin, and Goodman, 1962) and raised by struggle (Woodbury and Davenport, 1952), and are not responsive to acute administration of the anticonvulsant drug, diphenylhydantoin, in adult animals (Woodbury, 1954). The ECS threshold does however, appear to be sensitive to diphenylhydantoin in very young animals (Vernadakis and Woodbury, 1965). Furthermore, the effects of ECS-produced convulsions are not analogous to withdrawal convulsions. ECS produces elevated conditioning thresholds and state dependent learning (Nielson, 1968) while withdrawal seizures do not change these thresholds (Nielson, this report).

This review of brain excitability measures and inferences from those measures, was undertaken for the specific purpose of examining what the concept of brain excitability might mean. The review was not intended to be exhaustive of the literature, but rather to look at some recent and perhaps representative experiments into the mechanisms of drug action. The review should have made it clear that the term "hyperexcitability of the nervous system" has no meaning which can serve as a guide for research. Continued research into drug withdrawal mechanism with supposed hyperexcitability of the nervous system as the guiding theoretical principle, will only continue to produce fuzzy results.

There is one fundamental puzzle that continues to present problems of interpretation of the effects of drugs on behavior. This is the problem of tolerance or more specifically, a difference between the effects upon brain excitability and the effects upon the animal's behavior or cognitions. In this research we attempted to evaluate both. We came to the conclusion that changes in excitability level was not the basis for drug substitution since drugs, and drug combinations that adequately substituted for pentobarbital and maintained a state dependent CR did so at a variety of CR thresholds. Thus, the basis of drug substitution was not CR thresholds or brain excitability levels. Similarly, with repeated drug administration the CR thresholds did not change, yet tolerance to the drugs should have developed. We did not see any CR threshold shifts that suggested tolerance. Therefore we have concluded that CR threshold shifts are not the basis for tolerance. The same CR intensity maintained the response despite repeated doses of the same and cross tolerant drugs. The equivalence of drugs is dependent upon some as yet unspecified cognitive event. In this experiment the cats apparently evaluated the substitute drugs as producing the same state as the pentobarbital. The nature of this evaluation whether hedonic, cognitive or whatever, is not known, that such evaluations are known and reliable is known. Goldstein, Aronow and Kalman (1974) have commented

"...Curiously, the most reliable way of finding out if a new drug is addictive is to give it to addicts under controlled "blind" conditions and ask them if they like it! Addicts were able to identify morphine, heroin, and other narcotics and to distinguish them from barbiturates, amphetamines, and placebos with remarkable accuracy. If one were to select, on the basis of single doses, the most important single subjective response identifying a drug as being subject to morphine-like abuse, probably this measure would be whether the former opiate addict identifies the drug as an opiate ("dope"). If a new drug met with the approval of addicts, it was concluded that the drug would probably have a high addiction liability."

Thus, there appears to be some aspect of tolerance, that is not related to brain CR thresholds (as identified in this report) or to brain levels of narcotic drugs (in tolerant animals, much less interference with running behavior is noted than with controls at the same brain concentration (Goldstein et al., 1974). Tolerance is probably related to motor experience, while in the drugged state since, when the animal was trained in the drugged state, CR thresholds increased as pentobarbital dose was decreased; the opposite

effect that is obtained when the animal is trained in the non-drugged state. Thus tolerance is possibly the animal's cognitive evaluation of the consequences of its drugged experience and drugged state. What this cognitive re-evaluation can be is anybody's guess. However, it may be analogous to the reorganization of the visual world that is seen in people that wear prisms to chronically distort their visual field (see Held, 1968).



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